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U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)

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FEDERAL INSECTICIDE, FUNGICIDE AND  
RODENTICIDE ACT SCIENTIFIC ADVISORY PANEL  
(FIFRA SAP)

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OPEN MEETING TO CONSIDER AND REVIEW DRAFT  
FRAMEWORK AND CASE STUDIES ON ATRAZINE,

HUMAN INCIDENTS AND THE AGRICULTURAL  
HEALTH STUDY: INCORPORATION OF EPIDEMIOLOGY  
AND HUMAN INCIDENT DATA INTO HUMAN  
HEALTH RISK ASSESSMENT

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WEDNESDAY,  
FEBRUARY 3, 2010

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The Panel convened at 8:30 a.m. in  
the Lobby Level Conference Center of the U.S.

Environmental Protection Agency, located at  
One Potomac Yard, 2777 Crystal Drive,

Arlington, Virginia, Steven G. Heeringa,  
Chair, presiding.

FIFRA SAP CHAIR PRESENT:  
STEVEN G. HEERINGA, Ph.D.

DESIGNATED FEDERAL OFFICIAL PRESENT:

MYRTA R. CHRISTIAN, M.S.

FIFRA SAP MEMBERS PRESENT:  
JOHN R. BUCHER, Ph.D., DABT  
JANICE E. CHAMBERS, Ph.D., DABT, Fellow ATS  
GERALD A. LeBLANC, Ph.D.  
CAREY N. POPE, Ph.D.

KENNETH M. PORTIER, Ph.D.

FQPA SCIENCE REVIEW BOARD MEMBERS PRESENT:

JOHN C. BAILAR, III, M.D., Ph.D.

FRANK J. BOVE, Sc.D.

RICHARD GREENWOOD, Ph.D.

ELLEN B. GOLD, Ph.D.

SHELLEY A. HARRIS, Ph.D.

WILLIAM L. HAYTON, Ph.D.

CHENSHENG LU, Ph.D.

BETTE MEEK, Ph.D.

NU-MAY RUBY REED, Ph.D., DABT

JOHN S. REIF, D.V.M., M.Sc.

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8:30 a.m.

MS. CHRISTIAN: Good morning. My name is Myrta Christian. I am the Designated Federal Official for this FIFRA Scientific Advisory Panel.

I would like to welcome everyone to today's meeting to continue the discussion on the Draft Framework and Case Studies on Atrazine, Human Incidents and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment.

Again, I would like to thank the Panel, the presenters and the public for participating in this meeting. Also, I would like to remind one more time to everyone that the documents related to this SAP meeting are in the docket at regulations.gov, and the presentations from yesterday will be available in a few days.

I look forward to another day

1 filled with lively discussions and great panel  
2 participation.

3 At this point, I would like to  
4 introduce Dr. Steve Heeringa, Chair of the  
5 FIFRA Scientific Advisory Panel.

6 CHAIR HEERINGA: Good morning,  
7 everyone, and welcome back to a second day of  
8 this meeting of the FIFRA Science Advisory  
9 Panel.

10 Before we get underway with the  
11 proceedings, just a little summary of where  
12 our agenda will go this morning. We are still  
13 in the period of public comment. I mentioned  
14 yesterday afternoon that I would leave that  
15 open overnight in case there were any  
16 additional points of clarification and we did  
17 sort of push things along a little bit toward  
18 the end to get everybody in.

19 So, we'll open that up again just  
20 for a short period of time, any follow-up  
21 questions or issues on the public comment, and  
22 then we will turn back to the Environmental

1 Protection Agency staff for a wrap-up and  
2 summary in preparation for the Panel's turn to  
3 addressing the charge questions.

4 And I think I would like again  
5 this morning, just to go around. A few new  
6 participants have joined on the Panel. Dr.  
7 Pope.

8 But just to remind us of who we  
9 are, I am Steve Heeringa, the University of  
10 Michigan. I am an applied statistician. I'm  
11 the Chair of the FIFRA Science Advisory Panel  
12 and here predominantly to help with the  
13 meeting itself and running of the meeting.

14 I'll turn to my colleague on the  
15 left, Dr. Portier.

16 DR. PORTIER: Good morning. I'm  
17 Ken Portier, Director of Statistics, the  
18 American Cancer Society. I'm a  
19 biostatistician and member of the permanent  
20 panel.

21 DR. CHAMBERS: I'm Jan Chambers, a  
22 professor in the College of Veterinary



1 Medicine at Mississippi State University. I'm  
2 a pesticide toxicologist and I'm a member of  
3 the permanent panel.

4 DR. BUCHER: I'm John Bucher. I'm  
5 the Associate Director of the National  
6 Toxicology Program at NIHS. I'm a  
7 toxicologist by training and a member of the  
8 permanent panel.

9 DR. POPE: I'm Carey Pope. I'm  
10 Professor of Toxicology at Oklahoma State  
11 University, Center for Veterinary Health  
12 Sciences, and a member of the permanent panel.

13 DR. BAILAR: John Bailar, retired  
14 University of Chicago and now Scholar in  
15 Residence at The National Academies in the  
16 position of biostatistician/epidemiologist.

17 DR. MEEK: And I'm Bette Meek, and  
18 I'm Associate Director of Chemical Risk  
19 Assessment at the McLaughlin Centre,  
20 University of Ottawa, an interchange from  
21 Health Canada, where I manage several chemical  
22 risk assessment programs, and my background is

1 in toxicology risk assessment.

2 DR. GREENWOOD: I'm Richard  
3 Greenwood, Professor of Environmental Science  
4 at the University of Portsmouth. My expertise  
5 is in the area of mode-of-action of pesticides  
6 and in environmental monitoring.

7 DR. HARRIS: And I'm Shelley  
8 Harris. I'm an Associate Professor at  
9 University of Toronto and a Scientist at  
10 Cancer Care Ontario. And I'm an  
11 epidemiologist with a background in exposure  
12 assessment and toxicology.

13 DR. BOVE: My name is Frank Bove.  
14 I'm a Senior Epidemiologist in the Division of  
15 Health Studies of the Agency for Toxic  
16 Substances and Disease Registry, which is part  
17 of the Centers for Disease Control.

18 DR. LU: Good morning. Alex Lu  
19 from Harvard School of Public Health. I do  
20 pesticide exposure and cause/effect research.

21 DR. GOLD: Hi. I'm Ellen Gold.  
22 I'm Professor and Chair of the Department of

1 Public Health Sciences at UC Davis and Chief  
2 of the Division of Epidemiology there.

3 DR. HAYTON: Good morning. I'm  
4 Bill Hayton, Professor of Pharmacy at Ohio  
5 State University with an interest in  
6 pharmacokinetics.

7 DR. REED: Nu-May Ruby Reed,  
8 Toxicologist at the California Environmental  
9 Protection Agency. I do pesticide risk  
10 assessment.

11 DR. REIF: I'm John Reif. I'm an  
12 Environmental Epidemiologist from the  
13 Department of Environmental and Radiological  
14 Health Sciences at Colorado State University.

15 DR. LeBLANC: I'm Gerry LeBlanc.  
16 I'm Professor and Head of the Department of  
17 Environmental and Molecular Toxicology at  
18 North Carolina State University.

19 CHAIR HEERINGA: Thank you, members  
20 of the Panel. And before we return to our  
21 period of public comment, I'd like to turn to  
22 Dr. Steve Bradbury or Dr. Tina Levine if you

1 have any opening comments - oh, Dr. Anna  
2 Lowit.

3 DR. LOWIT: I thought you would  
4 start with public comments. We don't have any  
5 clarification. We went around the team, and  
6 no one had anything we wanted to clarify. We  
7 thought yesterday's discussion was excellent.

8 And just one point we wanted all  
9 of you to know that Dr. Michael Alavanja is  
10 available today and he's sitting back there,  
11 but he will not be available in the room  
12 tomorrow.

13 CHAIR HEERINGA: Thank you very  
14 much, Dr. Lowit.

15 At this point in time, I would  
16 like to return to our period of public  
17 comment. And we have one more public  
18 commenter who has approached Myrta Christian,  
19 the Designated Federal Official. It's Dr.  
20 Robert Silkin. And I think he can identify  
21 his affiliation, but I think he's with the  
22 Syngenta Group or -

1 DR. SILKIN: Thank you, Dr.  
2 Heeringa.

3 CHAIR HEERINGA: Panel members,  
4 there is a handout, I think, of Dr. Silkin's  
5 slides.

6 DR. SILKIN: Yes, there is a short  
7 handout, and there is a slide set, too,  
8 please.

9 My name is Bob Silkin. I'm a  
10 statistician formerly of Texas A&M University,  
11 and I'm now a consultant for Syngenta at this  
12 particular case. I consult for a lot of  
13 people, but I'm here today on behalf of  
14 Syngenta.

15 Dr. Bove yesterday correctly  
16 pointed out that the correlation plot that you  
17 see up here is really for the 18 CWSs that had  
18 SGA prevalence. And it does have one point  
19 for each of the CWSs.

20 In the data set itself, there is  
21 the number of births in each of those CWSs.  
22 And it's pretty obvious as you glance down

1     that column - I guess that's a pointer, but it  
2     doesn't matter.

3                 Second column from the right is  
4     the number of births. Fort Wayne is over  
5     16,000. Some of the others have around 200.  
6     So, they're not all equal size in terms of  
7     number of births.

8                 So, the question might be what  
9     would happen if you treat each of those births  
10    individually instead of just the CWS, and  
11    would that change anything? Obviously, it  
12    would re-weight the points.

13                Since I don't have the individual  
14    data, all I can do is basically do a weighted  
15    correlation where the weights would be the 233  
16    for Batesville and 255 for Bedford, etcetera.

17                And if I do that and redo the  
18    correlation, I still get a non-positive  
19    correlation. The values shown here, they're  
20    not really statistically significant, but  
21    they're not pointing in a positive direction  
22    either.

1                   This plot is what Excel gives me.  
2   If I jitter those points a little bit, and I'm  
3   not sure whether everybody knows what  
4   jittering is, but if I just add a small,  
5   normal deviate to each point, I can kind of  
6   move them around in Excel and give you an idea  
7   that some of those data points have a lot more  
8   individuals in them than others.

9                   That big blob there is really Fort  
10   Worth - Fort Worth? Fort Wayne. Sorry. I  
11   live in Texas now. I went to school in  
12   Indiana. I went through Fort Wayne on the way  
13   home.

14                  But, anyway, that's Fort Wayne,  
15   and you can see there's a couple of others,  
16   two or three others that have a much larger  
17   sample size than the other.

18                  A little bit of a sensitivity  
19   analysis. Since Fort Wayne is so dominant  
20   with 68 percent of the births, the question is  
21   what happens if you omit the Fort Wayne, which  
22   is hugely dominant? What does the rest of

1     them say?   Still a non-positive correlation.

2                 Further sensitivity analysis is in  
3     this slide you see one point kind of way over  
4     to the right.   That's Batesville.   And it has  
5     just a few - about 200 people in it.

6                 If you take that point out, what  
7     do you have left?   And you have almost just  
8     noise, but not a negative - small, negative  
9     correlation, not a positive correlation.

10                So, that was just a clarification.

11                CHAIR HEERINGA: Dr. Bove.

12                DR. BOVE: Well, there's still a  
13     major problem with this analysis.   First of  
14     all, I don't understand why you don't read the  
15     paper in use and see the analysis there.

16                It's an individual level analysis.  
17     They take into account the season of  
18     pregnancy, they have data from the  
19     municipality, they do a regression, a logistic  
20     regression.

21                My problem with the logistic  
22     regression, by the way, and we'll talk about



1 this later, is they use a continuous variable  
2 and they have strong assumptions for how the  
3 exposure-response curve looks.

4 But no matter how you slice the  
5 data when you look at it at an individual  
6 level with the information they had, with the  
7 information on individual potential  
8 confounding factors in all and they model it,  
9 they have a positive, although very mild, but  
10 positive association.

11 And no matter how many times you  
12 do this which uses less of the information in  
13 the study, I don't understand the point.

14 I think that if you read the paper  
15 and focus on the analysis done, you can see  
16 whether you think it's a strong association or  
17 weak association not looking at statistical  
18 significance, but looking at the actual point  
19 estimates, regression estimates and so on.  
20 Then looking at the confidence intervals, of  
21 course, and looking if there's an exposure  
22 response. And there are problems with the

1 paper on that level.

2                   You don't have to resort to this,  
3 which is using less of the information and  
4 really a distortion of the information in the  
5 paper.

6                   So, I have a hard time  
7 understanding why you're doing this exercise  
8 when there's plenty of information in the  
9 paper for which they'll criticize the paper if  
10 you want.

11                   The other thing is that when you  
12 look at Fort Wayne, they looked at Fort Wayne  
13 separately and they said - and they don't  
14 provide enough of the information for me to  
15 judge, but they said that the relationship  
16 they found with all the data was similar with  
17 Fort Wayne. Okay.

18                   So, I think they've dealt with  
19 these issues. I think this is a useless  
20 exercise. I think that what you need to do is  
21 look at the paper and decide whether you think  
22 that the effects they saw were important,

1 clinically important, biologically important,  
2 whatever, scientifically important or not.

3 DR. SILKIN: Well, you're quite  
4 correct that they had a lot more data than I  
5 do to work with. By not having the individual  
6 data, not having the individual confounders,  
7 all I can go by is what they say and what they  
8 put in the paper. I have no way of checking  
9 the validity of the confounders, the effects  
10 of the confounders.

11 I have their confidence intervals,  
12 and admittedly there are some problems just  
13 looking at the paper with what they did. And  
14 you're quite correct that this is not as good  
15 as what you could do if you had all the data,  
16 which they have and I don't have, yes.

17 CHAIR HEERINGA: Other questions of  
18 clarification for Dr. Silkin on his  
19 presentation?

20 Thank you. Thank you very much.

21 At this point in time, I'd like to  
22 turn to the panel. We've heard from a number

1 of public commenters yesterday afternoon.  
2 They offered different presentations on  
3 different topics. Some of them related to  
4 potential methodologies, some of them related  
5 to an overview and sort of summary of their  
6 interpretation of the charge questions.

7 Is there any questions of  
8 clarification that the panel would like to  
9 bring to - if you could just identify to whom  
10 and see if we can bring them up.

11 DR. REIF: John Reif. I have  
12 several questions for Dr. Alavanja that I'd  
13 like to have him address this morning.

14 CHAIR HEERINGA: Dr. Alavanja,  
15 well, he's actually with the EPA Group, too,  
16 so let's hold the questions.

17 Dr. Alavanja, since you're part of  
18 the EPA presentation, let's hold that for a  
19 follow-up. For the public commenters from  
20 yesterday, going once, going twice. If  
21 something comes up during the charge  
22 questions, we may be able to negotiate with

1 the EPA to bring somebody up to answer a  
2 question.

3 At this point, then, any final  
4 public comments at this point?

5 Okay. I want to bring the period  
6 of public comment to a close and turning to  
7 Dr. Lowit, if we can turn to some questions,  
8 follow-up questions for your staff, and then  
9 any comments that you would have.

10 DR. LOWIT: Sure.

11 CHAIR HEERINGA: That includes Dr.  
12 Alavanja too. So, Dr. Alavanja, I apologize  
13 for the formality, but I just want to make  
14 sure we kept everybody in the right balance.

15 Dr. Reif.

16 DR. REIF: Sorry I was out of  
17 order, but I would like to pursue a few  
18 thoughts with Dr. Alavanja regarding the  
19 potential for the agricultural health study to  
20 shed light on potential health effects of  
21 agrochemicals on reproductive outcomes.

22 So, most of the discussion

1 yesterday focused on the differences in  
2 exposure assessment and the way that exposure  
3 assessment was done in the agricultural health  
4 study versus the approach that the Agency  
5 uses.

6 But I'd like to ask Dr. Alavanja,  
7 if he would, to briefly describe the female  
8 members of the cohort with respect to their  
9 numbers, their distribution across the two  
10 states, and, to the extent that he recalls,  
11 the proportion of these women who actually  
12 work on a farm or who don't report work on a  
13 farm, that is who work off a farm. And then  
14 I've got another couple of questions.

15 DR. ALAVANJA: I'd be happy to  
16 answer that question.

17 I mentioned yesterday that there  
18 were three rounds of interviewing that went  
19 on, and all of the papers that we have  
20 produced thus far have utilized the exposure  
21 information from what we call Phase 3. The  
22 interviews started in 1993, and they went

1 through 1997.

2 That exposure information assumed  
3 that if you were an unlicensed individual, you  
4 didn't apply pesticides on the farm. And that  
5 was a mistake when it came to the spouses.

6 About 45 percent of the spouses do  
7 in fact assist their husbands on the farm,  
8 because the pesticide applicators are 97  
9 percent male in our study.

10 So, I made an incorrect assumption  
11 in Phase 1 that if you were unlicensed, you  
12 wouldn't apply. So, Phase 1 data is not  
13 robust with regard to the question of  
14 ascertaining exposure among the spouses. And  
15 that would be the critical group to look at  
16 for the reproductive outcome.

17 In Phase 2 and 3, I realized that  
18 we made a mistake, and we now ask for both the  
19 bystander exposure and also the direct  
20 occupational exposure. We will now start  
21 using Phase 2 and Phase 3 data along with  
22 Phase 1 data for exposure assessment, and so

1 we are now able to address that question more  
2 rigorously.

3 So, it's something that we will be  
4 doing. We didn't have the capability of doing  
5 until we integrated all of the exposure  
6 information from Phase 1, 2 and 3 of the  
7 questionnaires.

8 One, I guess, last remark is that  
9 for some outcomes we can look at the  
10 approximately 1500 farmer/applicators who are  
11 women in our study, but it's not going to pan  
12 out for the reproductive effects because it's  
13 just too small a group to look.

14 DR. REIF: What are the dimensions  
15 of the total number of women in the two states  
16 with all exposures?

17 DR. ALAVANJA: Just under 31,000  
18 individuals.

19 DR. REIF: So, I'm aware of some of  
20 the publications on the website predominantly  
21 done by your colleagues at NIHS, if I'm not  
22 mistaken.



1                   Has there been an effort to link  
2 birth records with the women in the AHS to  
3 validate perhaps the self-reporting of events  
4 with respect to pregnancy outcome?

5                   DR. ALAVANJA: Yes. There is a  
6 manuscript that is now in press that did that  
7 in the state of Iowa, and so we were able to  
8 validate the responses on births. We also  
9 found a few additional births that occurred  
10 usually right after the interview was given,  
11 and so we can do that in the future.

12                  But there is a potential rub that  
13 we're trying to work out in the next few  
14 months, and that is if someone was identified  
15 - what we did, 89,658 adults in the  
16 agricultural health study, when we interviewed  
17 the adults, we also asked about children in  
18 the family, and so we have the information  
19 from the parents.

20                  But for many of those individuals,  
21 they're now over the age of 18 and there's a  
22 question as to whether or not you can follow

1 those children up without getting informed  
2 consent from those individuals directly.

3 So, that issue is now - well, will  
4 soon be in front of our IRB to see if we can  
5 do that. It would be a great loss to us if we  
6 couldn't do that, and it also would be a great  
7 challenge for us with our budget, to go back  
8 and try to get informed consent from those -  
9 the number is over 35,000 children. So, that  
10 would be a real challenge for us to do that.

11 So, that is a potential problem  
12 that we have to address in the next year.

13 DR. BOVE: Let me ask a quick  
14 question on that.

15 CHAIR HEERINGA: Dr. Bove.

16 DR. BOVE: But you can see if some  
17 of those children had birth defects on the  
18 registry.

19 DR. ALAVANJA: In Iowa particularly  
20 since -

21 DR. BOVE: Yes, yes.

22 DR. ALAVANJA: - they have a very

1 well-developed birth defects registry.

2 DR. REIF: My final question has to  
3 do with exposure assessment particularly with  
4 respect to the women. And in the discussion  
5 yesterday, most of it focused on the pathways  
6 that are referable to the applicators, and  
7 rightfully so.

8 But in an environment like what we  
9 find in Iowa and probably in North Carolina,  
10 the probability of having agrochemicals find  
11 their way into groundwater certainly exists,  
12 and most farms rely on private wells for their  
13 domestic consumption.

14 So, my question is has there been  
15 any monitoring of private wells on the farms  
16 that are part of the agricultural health study  
17 with respect to agricultural chemicals, and  
18 are there any plans to do so if that has not  
19 been done to date?

20 DR. ALAVANJA: Dr. Mary Ward is an  
21 environmental epidemiologist who works in our  
22 branch and is interested in that topic, has

1 done work in other studies. She is working  
2 with us now.

3 We have the address information  
4 for all of the participants in the ag-health  
5 study, and most of those addresses have now  
6 been geocoded.

7 And so based on information that  
8 we can get from the U.S. Geologic Survey and  
9 such with regard to a lot of testing that  
10 they've done in the state of Iowa, Mary is  
11 doing a modeling exercise to determine where  
12 the high exposures were historically.

13 One would have to bring to bear  
14 what was grown in those areas, what was  
15 applied to those fields and what were measured  
16 in those wells. And she is doing an exercise  
17 that will try to incorporate all that, so that  
18 that type of research could be done.

19 As far as making current  
20 measurements, some current measurements are  
21 planned, but that would only get you so far  
22 because of the contaminants in the well would

1 change with time. So, it's really a longer  
2 period of time that one would have to  
3 characterize the exposure.

4 DR. REIF: And I think you're  
5 responding from the standpoint of a cancer  
6 epidemiologist primarily. But from a  
7 reproductive standpoint given the finite  
8 nature of the relevant exposure period, I  
9 would just suggest that one ought to think  
10 carefully about current exposure assessment  
11 followed by the prospective period of  
12 reproduction and the potential for some  
13 informative studies to be added to the  
14 agricultural health study, which of course is  
15 an incredibly rich data source. Thank you.

16 DR. ALAVANJA: If I could add just  
17 one - yes, I am thinking as - I always revert  
18 to thinking as a cancer epidemiologist, but I  
19 come up for fresh air and think about the  
20 question.

21 The issue still remains, though,  
22 the average age of the cohort and the women in

1 the cohort is now 56. So, it's getting very  
2 powerful for cancer studies, but it's getting  
3 less powerful for our reproductive studies.

4 Of course there's always a tail,  
5 you know, where there are younger women, but  
6 that would be a problem. Most of the new  
7 births have passed. We're not in that season  
8 any longer.

9 CHAIR HEERINGA: Dr. Harris.

10 DR. HARRIS: Shelley Harris.  
11 Yesterday you talked a little bit about the  
12 collection of PPE information and how you did  
13 that, I think, by different categories and  
14 classifications of pesticides. And I'm  
15 interested in whether you collected that for  
16 different activities such as spraying or  
17 mixing and loading or fixing equipment. And  
18 if yes, did you do it - is it chemical-  
19 specific information?

20 I have a couple other questions as  
21 well.

22 DR. ALAVANJA: The specificity to

1    which we're getting the information is far  
2    greater in Phase 2 and Phase 3.  We built on  
3    our experience from Phase 1, so that is the  
4    case that we are getting it in categories.

5                So, personal protective equipment  
6    is now routinely obtained for insecticide use,  
7    for herbicide use, fungicides and fumigants.  
8    And so we are doing it that way.

9                DR. HARRIS: So, you don't have a  
10   specific measure so farmers might put gloves  
11   on or an apron or a respirator, something to  
12   mix and load, but not to spray.  So, you don't  
13   have the data separately for activities.

14               DR. ALAVANJA: No, we -

15               DR. HARRIS: No.

16               DR. ALAVANJA: We have it for two  
17   broad categories.  We do actually have it for  
18   mixing and loading, and then for spraying.

19               DR. HARRIS: And was there any  
20   consideration so you have acre - you probably  
21   have a lot of information on acres and  
22   different types of crops and incorporating any

1 kind of measures of volume or acres sprayed or  
2 active ingredient into the intensity - or into  
3 the either exposure scores or do you multiply  
4 those times the intensity scores?

5 DR. ALAVANJA: The difficulty we  
6 found was that we couldn't get that  
7 information accurately 20 years ago. So, we  
8 resorted to those - resorted - we used those  
9 variables that we knew in our experience had  
10 shown us that we could ascertain those  
11 variables reasonably reliable for 30 years  
12 ago, 20 years ago.

13 Active ingredient is a very key  
14 variable, but we don't - we couldn't get that  
15 information on individuals for historic  
16 reasons. So, that's not going to be a part of  
17 our algorithm - or is not now, and we don't  
18 anticipate it being used.

19 If it was introduced actually,  
20 though, let's say in Phase 4 which we're  
21 planning, we could do other sorts of studies  
22 that are not cancer-related that might benefit



1 from that.

2 DR. HARRIS: But do you have some  
3 of their pesticide use information or their  
4 purchase records over the years historically?

5 DR. ALAVANJA: We believe that they  
6 have those records, but they're not actually  
7 interested - well, the vast majority of people  
8 sharing those records with us. I can  
9 speculate as to why that might be, but it  
10 hasn't been a success.

11 I think it's tied up with the fact  
12 that some of that was sort of their tax  
13 records. And sort of teasing that apart at an  
14 individual home, it wouldn't be something that  
15 - we have not been successful with it.  
16 There's some technique that one could use, but  
17 we haven't discovered it.

18 CHAIR HEERINGA: Dr. Reed.

19 DR. REED: Yes, I'm also interested  
20 in what kind of information that you use to  
21 come up with the numeric coding for some  
22 parameters in the exposure intensity level.

1 I guess sort of give you sort of  
2 the back of my head, why am I asking this  
3 question, might help. I was a little bit  
4 surprised yesterday with the comparison  
5 between the two methods, agency's and AHS  
6 method. They're so close, 3.7 and three.

7 And so I'm asking the question  
8 from that standpoint that I noticed that. And  
9 maybe you covered it yesterday and I was just  
10 not catching it right. You have taken into  
11 account many sets of data, including the PHED  
12 data, when you come out with the codes.

13 How heavily was PHED considered in  
14 coming up with the scoring or how similar your  
15 scoring would reflect what PHED data raises?

16 DR. ALAVANJA: I was part of this  
17 paper. But what Mr. Dosemeci who was the lead  
18 author on this paper did, he actually started  
19 with the PHED data, but the PHED data doesn't  
20 make a distinction between chemicals.

21 And so when you look at the  
22 world's literature, and he looked at over a

1 hundred papers that did exposure assessment,  
2 and some of those papers were certainly done  
3 under more realistic conditions, they were  
4 observing farmers at their work and measuring  
5 specific chemicals, so he would make  
6 adjustments to account for coming up with some  
7 type of weighted average of PHED along with  
8 the world's literature when it didn't fully  
9 agree with the PHED data. And so that's why  
10 there would be some differences between the  
11 two.

12 But I would like to point out one  
13 thing is that that paper Dosemeci did was  
14 published before most of our etiologic papers  
15 were done. We really were pushing hard to  
16 have a manuscript outlining our methods in the  
17 literature prior to what we were doing in the  
18 etiologic studies, and then commenting on  
19 that.

20 And we have yet not changed that.  
21 But if there are different weighting factors  
22 that we should incorporate, our intention is

1 to always do that with a published paper so  
2 that everyone will see our methods and make it  
3 fully transparent.

4 CHAIR HEERINGA: Dr. Alavanja,  
5 Steve Heeringa. A question about the  
6 population in the cohort trajectory over time.  
7 These were all licensed applicators. Some of  
8 them commercial, but some of them private farm  
9 applicators.

10 In the sequence of measures that  
11 you've made over time, have you determined the  
12 intensity with which they personally have  
13 applied these materials as opposed to the  
14 intensity with which they've applied on their  
15 particular farm?

16 The concern that I have is that -  
17 and maybe you can correct me - legally you  
18 have to be licensed to purchase this material.  
19 But I know from experience, you don't  
20 necessarily have to be licensed to drive the  
21 tractor that puts the spray down on the crop.

22 And to what extent the applicators

1 that you are measuring as your cohort may  
2 actually over time have reduced exposures  
3 personally transferring those exposures to  
4 children, to hands, to other people who are -  
5 is that sort of context captured in the ag-  
6 health study?

7 DR. ALAVANJA: I think we can  
8 always do a better job with that and it has  
9 been our concern. But one of the reasons we  
10 selected the states that we did, we wanted to  
11 go to states where it was a farmer-owner-  
12 operated farm. So that when you went to the  
13 farmer, in most cases they were the people -  
14 that was the person that did these activities.

15 And so that was sort of the  
16 underlying philosophy, and those two states  
17 were chosen from a group of many states in the  
18 Midwest and the southeast that could have been  
19 chosen, and others would meet the bill just as  
20 well.

21 But when we asked the question, we  
22 asked whether or not - we always ask did you

1 personally apply? And so we get the  
2 information about their personal application.

3 Over time there is some tendency  
4 to have commercial pesticide applicators apply  
5 the material to the farm, and so we get some  
6 of that information as well. But to this day  
7 in the ag-health study, it's still primarily  
8 the farmer themselves that are applying the  
9 materials.

10 And with regard to sons and such,  
11 and that does happen of course, whether or not  
12 that is accurately reported all the time, and  
13 there's a question about that, but for  
14 farmhands it tends actually not to be the  
15 case, seasonal workers and such, not to be the  
16 case yet in the agricultural health study.

17 CHAIR HEERINGA: Thank you. And  
18 the concern I guess that I had is to make sure  
19 that we capture exposure on the cohort numbers  
20 correctly. I know that we can't sort of split  
21 off to children and others, but it sounds like  
22 that's being done to the extent it can be.

1 Dr. Reed.

2 DR. REED: So, since most of the  
3 individuals in the database are farmers  
4 applying pesticides themselves, I would  
5 suppose that the repair frequency would be  
6 pretty substantial, right?

7 DR. ALAVANJA: Yes.

8 DR. REED: So, the scoring between  
9 zero and two, how do you assign the score? Is  
10 how frequently the repair makes the difference  
11 between zero and two or -

12 DR. ALAVANJA: If you consider the  
13 algorithm, the algorithm asks for the number  
14 of total days in a year that a person applies  
15 multiplied by years. And then the intensity  
16 factor is added onto that.

17 So, if a person was to repair  
18 their equipment and said "yes" to that, it  
19 would be a multiple times the number of days  
20 of application. So, it would be considered in  
21 that way since it's a multiple of that number.  
22 And so that's how it would enter into the

1 equation.

2 DR. REED: Thank you.

3 CHAIR HEERINGA: Thank you very  
4 much, Dr. Alavanja.

5 Any other areas that the panel  
6 would like to pursue clarification before we  
7 turn to the charge questions, on the  
8 presentations yesterday?

9 Dr. Reed.

10 DR. REED: Could I ask Shalu a  
11 similar question about -

12 CHAIR HEERINGA: Shalu Shelat and  
13 Jeff Dawson.

14 DR. REED: About the similarity  
15 between the two comparisons, 3.7 and three.

16 Do you have any take about why  
17 this is similar and any sense of speculation  
18 on the comparison?

19 MS. SHELAT: So, for the purposes  
20 of the case study at this point, I would just  
21 use an arbitrary example. We're not intending  
22 to make the conclusion that a lot of the



1 exposure rates will also be that similar.

2 I'm sure part of the reasoning is  
3 as Dr. Alavanja had mentioned, PHED is  
4 incorporated into the calculations for  
5 exposure rates. But until we look at it in a  
6 more holistic fashion, we really can't make a  
7 conclusion.

8 DR. REED: So in your agency  
9 calculation, part of it, and you're using  
10 PHED, you're taking the central tendency, not  
11 the upper bounds; is that correct?

12 MS. SHELAT: I'm going to defer  
13 that question to Mr. Dawson.

14 MR. DAWSON: I'm sorry. Could you  
15 repeat that? I apologize.

16 DR. REED: I was wondering in your  
17 comparison on the agency calculation site and  
18 you raising PHED, you are taking the central  
19 tendency, the average or the mean or the  
20 geometric mean or anything like that, not the  
21 extremes.

22 MR. DAWSON: Jeff Dawson. This

1 kind of came up yesterday. Dr. Portier asked  
2 a question around this issue. And the last  
3 couple years we've kind of very publicly said  
4 that there are some areas within PHED that we  
5 can improve.

6           So, we're actually involved in a  
7 large effort to essentially refine that  
8 database to be able to get at better  
9 addressing, for example, what the  
10 distributions of exposure look like and ways  
11 of ensuring and identifying subjects to  
12 monitor that can be related to - allow us to  
13 better answer the question, for example, of  
14 representiveness.

15           So, as that new information comes  
16 online, we'll be incorporating that additional  
17 information into this process. And part of  
18 the message I think we were trying to go over  
19 yesterday, was that we want to have some  
20 intense collaboration with the ag-health folks  
21 to refine that as we go and we get better  
22 information.

1                   Because, clearly, there are some  
2    areas within PHED that we need to improve and  
3    that are inherent because of the way that that  
4    database was created.

5                   DR. REED: Yes, I guess my question  
6    is specific to Shalu's analysis. When you  
7    access PHED and came up with the exposure  
8    estimate, you are taking it at the average  
9    mean or geometric mean and not the extremes,  
10   right? Not the bounds?

11                  MR. DAWSON: We're not using the  
12    bounds, right. We use the central tendency -

13                  DR. REED: Right.

14                  MR. DAWSON: - value that's  
15    inherent in the way that that system was  
16    created, right.

17                  DR. REED: I have another question  
18    about PPEs.

19                  Have you looked into whether the  
20    accounting of PPE in terms of percentage of  
21    protection is similar to what was used in the  
22    ag-health study?

1                   They have the 50 percent and so  
2   forth for various PPEs. Is that the same in  
3   the PHED or is it different? I thought some  
4   of them, I mean, in PHED would be greater than  
5   50 percent.

6                   MR. DAWSON: Absolutely. Actually,  
7   shortly after the initial unveiling, so to  
8   speak, of PHED, we actually did quite an  
9   extensive analysis where we looked at the  
10   variability of different types of personal  
11   protective equipment, for example, different -  
12   all the data we had with additional layers of  
13   clothing, and created an actual document where  
14   we looked at this and there's quite a range.

15                  So, we ended up using the values  
16   that we use based on that analysis, but it  
17   definitely ranges. For coveralls, for  
18   example, it ranged from 10 to 90 percent. And  
19   gloves as well.

20                  In cases where there are  
21   sufficient data, what we've done is segmented  
22   the data to just use, for example, here's the

1 folks that wear gloves and here's the folks  
2 that do not wear gloves. And we try to avoid,  
3 for example, in the way we do it, the use of  
4 protection factors.

5 But certainly the numbers they're  
6 using kind of overlay with what we see from  
7 the database.

8 DR. REED: But are different  
9 though, right?

10 I guess what I was trying to get a  
11 sense of is still the comparisons in that  
12 percentage of protection from PPE in PHED,  
13 could be expected to be different or the same  
14 compared to the percentage of PPE protection  
15 from use in the ag-health study.

16 MR. DAWSON: Well, they're the  
17 same.

18 DR. REED: They're the same.  
19 Exactly the same.

20 MR. DAWSON: The values that  
21 they're using certainly fit on the range of  
22 what we see as far as actual performance of

1 PPE based on the data that we have, right.

2 DR. REED: And that was used in  
3 PHED and - so, in terms of comparison of the  
4 two tracks, the PPE are the same - or  
5 protection of PPE are the same in terms of the  
6 percentage of protection?

7 MR. DAWSON: Right.

8 DR. REED: Okay.

9 CHAIR HEERINGA: Okay. At this  
10 point, I think I would like to move on to the  
11 charge questions. But before I do that, I'll  
12 turn - Dr. Lowit, anything that you would like  
13 to add before we turn to the charge questions?

14 You're free to add, of course,  
15 during that process too. Okay. Well, then I  
16 think that I would like to turn to the first  
17 of the charge questions. In setting this up  
18 for us, they pulled the old trick of subparts.  
19 So, what looks like four questions is probably  
20 more like 11 or 12 questions, but we'll  
21 recognize that in advance and move through  
22 them.

1                   So, it's actually an  
2   organizational strategy, I think. But in any  
3   case, we will start with the first question.

4                   And, Dr. Lowit, do you want to  
5   read it into the record for us, please?

6                   DR. LOWIT: Yes. Did you want me  
7   to read the preamble or just the question?

8                   CHAIR HEERINGA: Just the question  
9   is fine.

10                  DR. LOWIT: Okay. Okay. Good.

11                  Section II of the draft framework  
12   describes the major types of epidemiology  
13   studies along with their strengths and  
14   limitations, factors to consider when  
15   reviewing epidemiology studies, and ways to  
16   use epidemiology in risk assessment. Please  
17   comment on the soundness and completeness of  
18   these discussions. If appropriate, please  
19   include comments on additional factors for OPP  
20   to consider when evaluating the quality and  
21   weighing the utility of epidemiology studies  
22   in risk assessment/risk characterization.

1 CHAIR HEERINGA: Again for  
2 everyone, our process is there is a lead  
3 discussant assigned to each of these  
4 particular questions, and that individual will  
5 lead off followed by an assigned set of  
6 associate discussants, and then I'll open it  
7 up to the full panel for their comments.

8 And Dr. Bove is the lead  
9 discussant on Question 1.1.

10 Frank.

11 DR. BOVE: Okay. I have a whole  
12 lot of comments, and I can't go through them  
13 all. So, overall I'd say I'd like to see the  
14 section rewritten.

15 On Page 13, there's a list of  
16 study characteristics and they're fine. I  
17 would just want to add a few more.

18 One would be that the study have  
19 an appropriate interpretation of the findings.  
20 Of the studies we reviewed, they focus on  
21 statistical significance, findings that are  
22 elevated that are not statistically



1 significant are ignored, exposure-response  
2 relationships that are not statistically  
3 significant are ignored.

4 If the study does that, that's  
5 their problem. But in interpreting the  
6 studies, EPA doesn't have to follow what the  
7 authors of the study did. So, I would  
8 encourage EPA when they look at these studies,  
9 to not let statistical significance trump the  
10 magnitude of the association of the dose-  
11 response or any other consideration.

12 A second point to add to the list  
13 is appropriate evaluation of the exposure-  
14 response relationship. It's sort of tied with  
15 the first one, but also it's not sufficient to  
16 simply use a continuous variable in a logistic  
17 regression or to use tertiles, for that  
18 matter. It would be good to have an argument  
19 as to why you think that captures the curve.

20 The third issue is we hear a lot  
21 about confounding and it may occur in studies.  
22 Although, in my experience and the experience

1 of others, it's rare that there's considerable  
2 confounding in any study.

3 But putting that aside, it's not  
4 enough to just say that there may be the  
5 presence of confounding. I like to see  
6 sensitivity analysis. Just how important is  
7 the impact of confounding and other biases,  
8 for that matter? And there are methods to do  
9 that.

10 The fourth thing, it was raised  
11 yesterday, collinearity of contaminants. In  
12 my own work when I look at trichloroethylene  
13 in drinking water, oftentimes  
14 perchloroethylene is in drinking water. It's  
15 hard to distinguish the two.

16 So, you have to try to find study  
17 populations where the exposures vary enough so  
18 you can maybe tease out what might be the  
19 effective TC and what might be the effective  
20 PC or the other contaminants that seem to go  
21 together. And that's true of pesticides as  
22 well.

1                   So, you may want to encourage  
2 researchers to try to choose study populations  
3 where there's enough variability that that can  
4 get teased out.

5                   Now, on to the types of studies.  
6 Again, a lot of statements in here that I  
7 disagree with. For example, in a case control  
8 study, the controls have to be non-diseased.

9                   There are other control selection  
10 methods out there where the controls can have  
11 the disease of interest, even, and so I don't  
12 think you should make statements like that.

13                  The other thing about case control  
14 studies is that the exposures although we were  
15 interested in exposures in the past, they may  
16 not have to be too distant past for birth  
17 defects, for example. But in any case,  
18 exposures can be estimated using historical  
19 exposure reconstruction methods, which is  
20 using environmental monitoring and  
21 sophisticated modeling to try to do that.

22                  And so some of the problems that

1 people raise about case control studies can be  
2 - would not be a problem if you estimate  
3 exposure in that fashion.

4 A more serious problem in this  
5 section is about cross-sectional studies.

6 Many cross-sectional studies use historical  
7 information on exposure so temporality can be  
8 established, but the key feature is not - of  
9 a cross-sectional study is not that exposure  
10 and disease are measured at the same time.

11 The key feature of a cross-  
12 sectional study is it measures prevalence and  
13 - prevalence of disease, prevalence of  
14 symptoms, prevalence of biomarkers. Okay.  
15 So, that really is the key element, not that  
16 they're measuring exposure and disease at the  
17 same time.

18 And one of the advantages of the  
19 cross-sectional study because it's evaluating  
20 prevalence, is it can measure these  
21 biomarkers. They're not routinely collected.  
22 So, that's a very important advantage of

1 cross-sectional studies that can't be done  
2 maybe in other studies unless there's a lot of  
3 money put into a prospectus study to do these  
4 kinds of measurements over time, but there are  
5 drawbacks.

6           And the key drawbacks of a cross-  
7 sectional study are you're studying a survivor  
8 population. And that includes births. Births  
9 are a cross-section. Okay. You have to  
10 survive to birth in order to have a small for  
11 gestational age birth or a birth defect,  
12 unless you look at spontaneous abortions and  
13 other miscarriages and look at birth defects  
14 among them.

15           So, it's a survivor population.  
16 And that means that if the exposure affects  
17 those who don't survive. If the current  
18 employees in a workforce of those who can  
19 withstand the exposure and the people who  
20 couldn't have already gone and you go in and  
21 measure, you're measuring a survivor  
22 population. So, there are problems with that.

1 That's the first drawback with a cross-  
2 sectional study.

3 Second is that prevalence is a  
4 function of incidents and duration. So, the  
5 question is, is the exposure increasing  
6 incidents or is it increasing duration?

7 So, those are the two key elements  
8 of a cross-sectional study not really  
9 reflected in the paper.

10 Ecologic studies, there are good  
11 and bad ones. And I think even the bad ones  
12 sometimes we can learn something from. I  
13 think some of the presentations yesterday  
14 showing that there's seasonal effects even in  
15 low-atrazine areas is interesting. So, you  
16 can even learn something from a not very well-  
17 conducted ecologic study. But I think we have  
18 to figure out which ones are good and which  
19 ones aren't for this purpose. They're not all  
20 bad.

21 But a key element of an ecologic  
22 study, and this is where I think people get

1     confused, is that exposure is assigned to a  
2     population. We usually have variables such as  
3     the percent of the population exposed, the  
4     percent of the population who smoke, where we  
5     use mean, the average income of the population  
6     or average pack years smoking or average  
7     smoking sales or something of that sort.  
8     That's how exposures are defined in the  
9     ecologic study. It stays at the group level.

10             The Villanueva study the EPA  
11     considered an ecologic study, it isn't.  
12     Exposures are defined at the individual level.  
13     The individuals are characterized by the  
14     municipality serving them. The municipality  
15     has information to show that the water is  
16     uniformly distributed. So, the quality of  
17     that water is from one source and it's the  
18     same for everybody. So, a hundred percent of  
19     the people can be characterized in that  
20     population. It's an individual level study.

21             Now, some studies go from there  
22     and then start using ecologic variables to

1 control for confounding. That's a bad move,  
2 but that wasn't done in the Villanueva study.

3           There are other issues around  
4 ecologic studies besides the problem with  
5 exposure. Ecologic biases also affect how  
6 confounders are adjusted for, and it makes it  
7 more difficult to adjust for individual level  
8 confounders if you try to adjust for them  
9 using ecologic confounder information. So,  
10 those are some of the issues there.

11           We'll move on to the next part of  
12 the document, which is important scientific  
13 factors to consider, and talk about the  
14 exposure assessment section which contrasts  
15 direct and indirect - so-called indirect  
16 measures of exposure.

17           Direct is biomonitoring and  
18 personal monitoring. Indirect is historical  
19 records, questionnaires and environmental  
20 monitoring. And the problem with direct  
21 approaches and the benefits actually of so-  
22 called indirect approaches, is that it's



1 difficult to use direct approaches when your  
2 interest is in past exposures. Especially  
3 distant past exposures.

4                   On the other hand, an approach  
5 that uses environmental monitoring and  
6 sophisticated modeling, which in my agency we  
7 call historical exposure reconstruction, is a  
8 very important way of dealing with past  
9 exposures. We've used it in drinking water,  
10 we used it at Hanford for estimating iodine  
11 exposures. We've used it in a number of other  
12 areas. Mostly drinking water, but we also  
13 used it in air pollution as well.

14                   It's a very good, robust way of  
15 estimating past exposures. You can get  
16 quantitative information that's useful for any  
17 risk assessment you want to do. So, I think  
18 that that needs to be emphasized in this  
19 section.

20                   Again, historical records and  
21 questionnaires can estimate quantitative  
22 levels of exposure. It's not just true that

1 they can be qualitative, and it's been done.

2 Now, some of the problems with  
3 direct methods, on the other hand, as I said,  
4 they're not very good for past exposures, but  
5 they may not even capture the full range of  
6 exposures.

7 Unless you have that personal  
8 monitor on you for quite a long time, I mean  
9 you change over time and you may miss that.  
10 And besides, you're wearing a personal monitor  
11 and it may affect your behavior because you're  
12 wearing it. So, you may change your behavior  
13 because you're wearing that personal monitor,  
14 or you may change your day-to-day habits and  
15 you need a diary.

16 So, you need a questionnaire to go  
17 along with - so, you need an indirect  
18 measurement in order to go along with the  
19 direct measurement.

20 So, these are some of the  
21 complications that are not reflected in that  
22 section that need to be reflected.

1                   Confounding, substantial  
2    confounding occurs rarely. Even when you look  
3    at lung cancer and smoking and you look at an  
4    occupational exposure to compare workers to  
5    the general population, the amount of  
6    confounding usually found is less than 20  
7    percent. And that's the most confounding you  
8    could probably find in a study.

9                   So, again, people raise the issue  
10   all the time. It's important to figure out  
11   what the impact of confounding is. And that  
12   can be done by sensitivity analyses.

13                  As we heard about the agricultural  
14   health study that there is no confounding in  
15   that study, that does not surprise me.

16                  The other issues, you have to be  
17   careful about what you put into a model. I'm  
18   a little concerned about putting seasonality  
19   in the model. Seasonality, there are a lot of  
20   factors involved in seasonality. In areas  
21   where there's low atrazine exposure,  
22   seasonality may be affected by such things as

1 air pollutants, trihalomethane and other  
2 disinfection byproducts because they're  
3 seasonal as well. But in the areas where  
4 there's pesticide use, seasonality could be  
5 affected by the pesticides themselves. Okay.

6 So, you put seasonality in a  
7 model, you may be adjusting for exposure. And  
8 when you do that, you're biasing your point  
9 estimate towards null. That's a bias.

10 Bias one way, you know, everyone  
11 focuses on that, but bias the other way is  
12 just as important. You want the right answer.  
13 Okay. So, you have to be careful about that.

14 Another study put a variable in  
15 there for percent of the land around the house  
16 that had crops. Again, I'm worried that  
17 they're adjusting for the exposure itself and  
18 making an already difficult study, a study  
19 that has difficulty estimating the effect,  
20 even more difficult. So, they need to be  
21 careful about what variables they put in the  
22 model.

1                   A few more points and then I'll  
2 get out. Effect modification and confounding,  
3 totally different ideas. Totally different.  
4 Effect modifiers do not have to be  
5 confounders, and in fact many aren't.

6                   But most importantly, I think  
7 confounding is a bias and we want to minimize  
8 that. Effect modification is a hypothesis.  
9 You want to design a study to evaluate that  
10 hypothesis.

11                  Some studies look at all kinds of  
12 effect modifiers and it's a fishing  
13 expedition. But really a study if it really  
14 wants to evaluate effect modification, has to  
15 be designed with enough statistical power to  
16 evaluate effect modification. That really  
17 needs to be stated here.

18                  There are also issues of  
19 statistical analysis that aren't mentioned  
20 such as if you put a lot of variables in a  
21 model, you may get statistical bias. That  
22 means the odds ratio you get, for example, may

1 be inflated because the model just can't  
2 handle all those variables, in a nutshell. Or  
3 if you use conditional methods, there may not  
4 be enough discordant sets or pairs and you get  
5 inflated odds ratios.

6 So, you have to be careful, again,  
7 of what you try to put in a model and what you  
8 don't.

9 Finally, two more points. One,  
10 interpretation of null studies. Again, the  
11 two major causes of null studies are exposure  
12 misclassification bias, and the second cause  
13 is lack of statistical power especially if  
14 you're focusing on only statistically-  
15 significant results.

16 And in birth defect studies when  
17 they use birth certificates as mentioned in  
18 these studies, you do have under-ascertainment  
19 and you can expect they're probably reduced  
20 because of that.

21 Finally, I think that epi studies  
22 have been used in all stages of risk

1 assessment, in the TC risk assessments, both  
2 the draft and the current. In the draft one,  
3 a drinking water study in New Jersey was used,  
4 for example. In the recent one that's now  
5 being considered, an occupational study of  
6 kidney cancer is just one example. But epi  
7 studies have been used in quantitative risk  
8 assessment, and should be used. And I think  
9 that's where I'll stop.

10 CHAIR HEERINGA: Thank you, Dr.  
11 Bove.

12 Dr. Meek.

13 DR. MEEK: Thanks very much. It's  
14 difficult to add an awful lot after that very  
15 extensive discussion, but my sense was that in  
16 this context, the text provided rather an  
17 overview, generically, the strength and  
18 weaknesses of various types of epidemiological  
19 studies, but didn't necessarily do so in a  
20 context specific to experience on pesticides,  
21 with the possible exception of the exposure  
22 questions.

1                   And my sense, also, was that while  
2   the case studies were helpful, it might have  
3   been more informative to include an indication  
4   of the extent and nature of reliance upon  
5   epidemiological or incidents data for a range  
6   of pesticides across the program to get a feel  
7   for that in previous assessments.

8                   And based on our experience in  
9   industrial chemicals and really following on  
10   from what Dr. Bove has said, the use of  
11   epidemiological data and risk assessment  
12   necessarily varies depending not only on the  
13   nature and quality of the studies, but the  
14   results, whether or not there is evidence,  
15   robust evidence of an effect in humans.

16                  For example, if we have evidence  
17   of an increase in a particular effect in  
18   humans based on robust epidemiological data in  
19   a population to which exposure has been well  
20   characterized and for which there is weight of  
21   evidence for causality, we would necessarily  
22   favor the use of those data in the dose-



1 response characterization.

2           On the other hand, if we have a  
3 negative epidemiological study for an effect  
4 which we consider to be relevant to humans  
5 based on toxicological and mode-of-action  
6 data, we might use this information to bound  
7 dose-response estimates from animal studies.

8           There's different ways to use the  
9 epidemiological data depending upon your  
10 confidence therein.

11           I had a couple of comments on the  
12 interpretation of null studies. It seems  
13 really important to mention in addition to the  
14 points that have already been mentioned, that  
15 without information on mode-of-action they are  
16 exceedingly difficult to interpret, unless,  
17 for example - if you take a particular end  
18 point, for example, for cancer, there is some  
19 understanding in mode-of-action for tumors  
20 induced in animals. It's unclear where tumors  
21 might manifest in humans and site concordance  
22 can't necessarily be assumed.

1                   And, also, the power to detect the  
2   effective interest is always critical  
3   interpretation of null studies and often never  
4   formally addressed. So, that's an issue. And  
5   then there's also the publication bias to  
6   exclusion of null studies that needs to be  
7   taken into consideration.

8                   Another point I think that it  
9   seems - and we'll get into this probably a  
10  little bit later in responding to some of the  
11  other questions, it also seems important to  
12  emphasize in relation to biomonitoring, that  
13  selection of relevant biomarkers of exposure  
14  and effect based on the toxicological database  
15  particularly that on mode-of-action, enables  
16  much greater likelihood of meaningfully  
17  integrating the epidemiological and  
18  toxicological databases.

19                  And I had a couple of comments on  
20  cross-sectional studies as well, particularly  
21  in the context of prevalence versus incidents.  
22  But I think they've been adequately covered

1 and I'll stop there.

2 CHAIR HEERINGA: Thank you, Dr.

3 Meek.

4 Dr. Gold.

5 DR. GOLD: Thanks. I have a few

6 things to add. I think the prior two speakers

7 have been pretty complete, but my sense was

8 that the exposure assessment part of this was

9 a little more fleshed out even though it had

10 some issues, than some of the other parts

11 where epidemiologists, I think, focus their

12 attention. And so, I would agree that this

13 section needs some work.

14 One really minor point is I think

15 in citing some of the references, some of them

16 are old editions of books that ought to be

17 updated. That's a really minor point.

18 But with regard to the particular

19 studies, I think that's where I focused most

20 of my attention. As I said, the exposure

21 assessment is sort of one part that we focus

22 on in epidemiologic studies, but a major focus

1 is how we select the people that go into the  
2 study so that we get a representative sample  
3 with regard to exposure.

4                   And so if you want to look at case  
5 control studies, you want to make sure that  
6 you have a representative group of cases at  
7 least with well-defined criteria so you can  
8 say something back to whom you can generalize  
9 on the basis of these and that they're not  
10 bias with regard to exposure, similarly, with  
11 controls that you select.

12                   So, we often go into detail when  
13 we're writing about how we select people to be  
14 in these studies, about what the inclusion and  
15 exclusion criteria are so that people who are  
16 evaluating the study know to whom they can  
17 generalize.

18                   I also thought that under case  
19 control studies, some mention of talking about  
20 newly diagnosed cases as opposed to using  
21 prevalent cases ought to be included. It's a  
22 similar issue about whether you're looking at

1 exposures that were related to survival or if  
2 you're looking at exposures that are related  
3 to the occurrence of the disease.

4 Also, I thought some attention on  
5 how you collect data in terms of making sure  
6 that it's similarly collected in cases and  
7 controls and exposed and unexposed. And if  
8 you're doing cohort studies, that you do it at  
9 the same intervals and in the same way. These  
10 are, you know, sort of basic fundamental  
11 things.

12 I think paying attention to  
13 attrition in cohort studies so that, again,  
14 you can generalize from the results and making  
15 sure that attrition is minimized and  
16 participation bias is avoided.

17 Also in the context of avoiding  
18 bias, that observers are masked as to the case  
19 control status, their exposed and unexposed  
20 status, they're masked to hypotheses that are  
21 being tested.

22 And also under cohort studies in

1 the analysis section, just saying that the  
2 appropriate analyses are undertaken is sort of  
3 a minimalistic approach. But that you're  
4 using the maximum amount of information from  
5 those studies so that if people are lost or  
6 censored, that you use all the possible data  
7 that you can in longitudinal studies.

8 I don't think I have much to add  
9 about cross-sectional or ecologic.

10 One minor - well, it's not a minor  
11 point, but it was touched on. I just want to  
12 say one more sentence about it that when we're  
13 controlling for confounding the ecologic  
14 studies, again it's often at the group level,  
15 not at the individual level. And so, again,  
16 the results that you get may not be  
17 applicable.

18 I also thought it was interesting  
19 that I didn't see - maybe I missed it - any  
20 mention of nested case control studies or case  
21 cohort designs, which are really powerful and  
22 useful tools and perhaps haven't been used as

1 fully as they could.

2           They could certainly be used in  
3 the agricultural health study, and there are  
4 other cohorts around where specimens have been  
5 collected and stored. Lots of cohort studies.  
6 I think this is an opportunity, actually, that  
7 hasn't been fully explored or used.

8           I agree with the comment about  
9 being able to get quantitative data from  
10 historical records, and it's been done many  
11 times.

12           Let's see. I think that's it for  
13 now.

14           CHAIR HEERINGA: Thank you, Dr.  
15 Gold.

16           Dr. Portier.

17           DR. PORTIER: It's always good to  
18 go third or fourth, and they cover all the  
19 good stuff. So, then you have to go looking  
20 for something different.

21           A general observation, many of the  
22 issues we're discussing relating to the

1 factors to consider when evaluating the  
2 quality and utility of epidemiology study  
3 results, are the same factors that medical  
4 clinicians face when trying to translate  
5 epidemiology study results to clinical  
6 practice.

7                   And I found an article I'll  
8 reference in the paper here, where they used  
9 epi data to guide clinical practice in the  
10 review of cardiovascular disease and combined  
11 oral contraceptives.

12                   And it was interesting because  
13 they reviewed 74 epidemiology studies, and  
14 concluded that seven of those 74 were relevant  
15 for a clinician to use in practice. And  
16 actually five of them were directly useful,  
17 and the other two might be useful if they re-  
18 analyze the data.

19                   And I thought in light of a lot of  
20 our discussion, I think the clinicians are  
21 doing the same thing you're doing and seeing  
22 the same results, that epi studies in general



1 aren't always directly useful.

2                   So, this got me thinking about  
3 what questions I might ask when screening epi  
4 studies for their relevance to risk  
5 assessment, which is kind of the utility part  
6 of the question here.

7                   So, I came up with some suggested  
8 questions, some of which are implied in the  
9 discussion of Section 2, but it might be  
10 better to be kind of a little more direct and  
11 say here are the kind of questions that EPA  
12 would be asking when we look at an epi study  
13 in general.

14                   So, was the epi study conducted in  
15 a hypothesis generating or hypothesis testing  
16 mode?

17                   And I have an aside to myself, we  
18 all agree that it's inappropriate and  
19 misleading to use data to develop a  
20 hypothesis, and then the same data to test it.

21                   But unfortunately when you read  
22 the conclusions of many of the hypothesis-

1 generating epi studies, it's like the authors  
2 forgot this point. Right?

3 And so I think the point Dr. Bove  
4 has made about really understanding the  
5 interpretation of the study, this relates to  
6 this. That if it's really an exploratory  
7 study, the discussion should be in that  
8 context. But often the discussion is very  
9 confirmatory sounding, and then there's a  
10 disconnect.

11 I've noticed this in a lot of -  
12 when you read a lot of the literature  
13 critically for its utility in risk assessment,  
14 I try not to read the conclusions. I read the  
15 methods and make sure I can understand what  
16 they actually did.

17 Was the method of assessing  
18 exposure valid? Has there been some attempt  
19 to compare the exposure method to actual  
20 exposure? Was the method of assessing  
21 exposure reliable, an accurate measure of -  
22 was it an accurate measure of actual exposure

1 or is there a bias involved in there? Was the  
2 method of assessing health outcomes valid and  
3 reliable? On one extreme was it confirmed  
4 with histopathology or reading medical  
5 records?

6 It wasn't really discussed that  
7 much about the health outcome confirmation  
8 part, but that's really another important part  
9 of an epi study. Do we really know that they  
10 have the condition that they say they have?

11 Did the study collect appropriate  
12 information on related and confounding factors  
13 such as cultural, behavioral, dietary and  
14 health factors, and related co-morbid  
15 conditions?

16 I'm always reminded that health  
17 conditions rarely occur alone. So, we're  
18 talking cancer, but they might also have  
19 diabetes and heart disease and all kind of  
20 other conditions. And those have a lot of  
21 impact on the health outcomes.

22 Factors that are known to impact

1 the health condition of interest as well as  
2 the factors that could impact exposure, we've  
3 had a little bit of discussion about that  
4 here.

5 Did the study measure the  
6 population or individual it's intended to  
7 measure? So, selection bias and  
8 generalizability are the issues here.

9 How does the study population  
10 relate to the universe of potentially exposed?  
11 So, the section talks about generalizability,  
12 but it's really important to make that  
13 relationship between what we studied and who  
14 we think to infer this to, who we want to be  
15 able to - so, it's Iowa and North Carolina,  
16 but really it's corn growers in the whole  
17 continental U.S. and Canada that we're trying  
18 to really make the inference to, and how do  
19 those two populations relate?

20 Did the study examine individuals  
21 from a wide range of exposures, including both  
22 those with high expected doses and those with

1 low expected doses?

2 This affects our ability to detect  
3 the dose-response and our ability to  
4 generalize. So, if we only study a population  
5 that has low doses, we're only going to  
6 generalize the populations with low doses.

7 Did the study include populations  
8 or individuals not exposed? In my mind,  
9 that's kind of the negative control concept in  
10 an experimental setting. So, we might do that  
11 in a before and after kind of study.

12 Can we say something about birth  
13 defects in the 1920s to the 1940s compared to  
14 the 1980s and 1990s? If they have the same  
15 seasonal patterns, that weakens the results  
16 from the study.

17 Do the exposures examined in the  
18 study relate to past or current situation?  
19 This relates to the issue of acute versus  
20 chronic exposures, the targeted health end  
21 point.

22 Some of the things that were

1 brought up yesterday by Dr. Bailar about, you  
2 know, is the health effect related to  
3 exposures that occurred 20 years ago or  
4 exposures that occurred last week? That's a  
5 critical issue.

6 And finally, did the study collect  
7 information on sufficient numbers of  
8 individuals to have adequate power for  
9 preselected health effect differences between  
10 the different classes of exposed individuals?

11 In other words, does the sample  
12 size take into account the rareness of the  
13 target health effect in the study population?

14 You rarely see epi studies talk  
15 about sample size determination like you'd  
16 expect to see in a randomized clinical trial.  
17 But that kind of thinking should occur at the  
18 design phase, and it should be reflected in  
19 the discussion of the methodology of the  
20 paper.

21 And finally, a minor thing. In  
22 Section C, the first paragraph on Page 20 of

1 the white paper, there's a statement about how  
2 high-quality studies with robust exposure  
3 assessment may be used to estimate risk  
4 quantitative.

5 And then that statement is  
6 qualified to indicate that most epidemiology  
7 studies suffer some limitation in size, scope,  
8 exposure assessment or data analysis which  
9 prevent their use in quantitative risk  
10 assessment. And this is referenced in  
11 Caledron (2000).

12 And I agree with this, but I think  
13 you need to support the statement in the  
14 document by providing at least one example of  
15 an epi study that really provided  
16 significantly the quantitative risk  
17 assessment.

18 And I have a reference here to an  
19 example of, say, the NIOSH dioxin study where  
20 they did heavy-duty biomonitoring and careful  
21 study design. And when you get finished, you  
22 really have that gold standard-type study.

1                   And having an example of a gold  
2   standard study in the white paper helps  
3   everybody kind of think this is, you know,  
4   this defines what I think is really good,  
5   useful epi data. And I think I'll quit on  
6   that.

7                   CHAIR HEERINGA: Thank you very  
8   much. Comments from other members of the  
9   panel in response to this question?

10                  Dr. Bailar.

11                  DR. BAILAR: I have two comments.  
12   Both rather brief.

13                  The first is that we tend to think  
14   of ecologic studies as being in sharp  
15   distinction to studies that have individual  
16   measurement of exposures and outcomes, but in  
17   fact there's a gradation between these.

18                  You can start with a pure ecologic  
19   study, maybe statewide incidents rates,  
20   statewide exposure levels, but then you go to  
21   municipalities. You come somewhat closer to  
22   individual exposures and outcomes.



1                   You could go from there to water  
2 sources within the municipality, to  
3 households, and finally to individuals. Where  
4 do you draw the line?

5                   I don't think it makes sense to  
6 actually draw a line there, but rather to  
7 treat this as a continuum. And I'd like to  
8 see that reflected in the document.

9                   Now, the other thing is just a  
10 brief expansion on the point Dr. Portier made  
11 about the difference between hypothesis  
12 generation and hypothesis testing.

13                  There are times when you really  
14 can't do what he suggests. A good example is  
15 in animal tests of - a long-term animal test  
16 of a new potentially toxic agent where you  
17 have the results of the animal test and that's  
18 all you've got. That's the only game in town.  
19 And you have to use those data in whatever way  
20 you can, then, to come up with estimates in  
21 testing the hypothesis that there is an  
22 effect. Thank you.

1 CHAIR HEERINGA: Dr. Reif.

2 DR. REIF: Just a few comments  
3 about the general writing of this section on  
4 the use of epidemiology in risk assessment.

5 I do believe that the whole  
6 section could be strengthened, it could be  
7 more explicit. The definitions of various  
8 terms I think in places, could be improved  
9 upon using standard references to be very  
10 clear about confounding, effect modification,  
11 etcetera.

12 One place where I think this  
13 document deserves some substantial exposition  
14 is in the issue of exposure misclassification,  
15 because this is bound to be a predominant  
16 problem in all of the epidemiologic efforts  
17 that have been made in the past and they're  
18 going to be made in the future.

19 So, a thorough exposition of the  
20 issue of misclassification, differential and  
21 non-differential misclassification, the  
22 effects of those errors on the risk

1 assessments, including probably a table as  
2 also one can find in standard text, would be  
3 very, very helpful.

4                   Differentiating misclassification  
5 of exposure from misclassification of  
6 confounders would be helpful. Differentiating  
7 non-differential misclassification of a  
8 dichotomous variable from a variable with  
9 multiple levels of exposure would be helpful  
10 because these, again, are very, very prevalent  
11 issues in doing any kind of environmental  
12 epidemiology, and continue to be one of the  
13 major sources of error in whatever direction  
14 the error occurs away from the truth so that  
15 the document could be improved substantially  
16 in that area.

17                   Another general comment in places  
18 in the document that the writers used terms  
19 like "ecologic" and "retrospective," that is  
20 really an improper characterization of  
21 epidemiologic research.

22                   The term "retrospective" has a

1 number of meanings and applications in  
2 epidemiologic research. For example, in case  
3 control studies which are usually thought of  
4 as retrospective, there is sort of a  
5 pejorative tone in parts of the document that  
6 suggests that case control studies because  
7 they are - because exposure is often  
8 ascertained retrospectively, are somehow  
9 inferior. And that is really an over-  
10 simplification of the strengths and weaknesses  
11 of case control studies.

12 Well-done case control studies  
13 that pay attention to various forms of bias,  
14 selection bias, potential confounding and  
15 other forms of bias, are extremely informative  
16 and have been used extensively by  
17 epidemiologists in a variety of arenas for  
18 many years. And, in fact, are probably the  
19 most commonly performed form of epidemiologic  
20 research.

21 So, I think that the writers  
22 should be very, very careful about the use of

1 terms like "ecologic" and "retrospective."  
2 Lumping those two terms is really a distortion  
3 that leads to interpretations that are not  
4 sound and not based on good epidemiologic  
5 practice and research methods.

6 CHAIR HEERINGA: Dr. Chambers.

7 DR. CHAMBERS: I'd like to respond  
8 to the second point Dr. Bailar made and  
9 respond from the standpoint of an  
10 experimentalist with respect to hypothesis-  
11 generating and hypothesis testing experiments.

12 In a well-designed animal study,  
13 the only thing that should be different should  
14 be the chemical of interest if it's a  
15 toxicology study. And there shouldn't be a  
16 lot of other factors going on, confounders and  
17 so forth like that.

18 So, I understand your point, but I  
19 think the epidemiology point that Dr. Portier  
20 was trying to make is an entirely different  
21 situation when you've got all those other  
22 confounders involved in human populations.

1 CHAIR HEERINGA: Any comments?

2 DR. REIF: That comment really  
3 emphasizes the need to be very explicit about  
4 confounding in this document. Because to the  
5 non-epidemiologist that thinks about  
6 epidemiologic research, confounding is  
7 probably almost the first word that comes to  
8 mind.

9 So, a very precise definition of  
10 "confounding," the requirements for  
11 confounding - actually, both the exposure -  
12 relationship to the exposure to the outcome,  
13 the causal pathway, are all important elements  
14 of confounding.

15 And what the worry is, is that we  
16 have in epidemiology, always the possibility  
17 of unrecognized confounding and unmeasured  
18 confounding, and those are the really more  
19 pressing issues. Because I think the ones  
20 that we recognize and that we take pains to  
21 incorporate into studies and into analyses are  
22 dealt with, can be dealt with effectively.

1                   It's this uncertainty about the  
2 residual unmeasured confounding that needs to  
3 be also emphasized in the document. Because  
4 in many epidemiologic studies, that may be the  
5 area that we don't address adequately.

6                   But I think a very precise  
7 definition to avoid this tendency to talk  
8 about potential confounders as sort of  
9 inherently biasing a variety of epidemiologic  
10 studies, in fact, all epidemiologic study  
11 designs, is a dangerous - perhaps a dangerous  
12 misconception that the author should attempt  
13 to correct in the document.

14                  CHAIR HEERINGA: Dr. Gold.

15                  DR. GOLD: I should have started my  
16 comments, I think, by commending the EPA on  
17 undertaking this effort because I really  
18 welcome the idea that you're willing to  
19 consider epidemiologic studies in your risk  
20 assessments. I think it's really important.

21                  So, I think our comments need to  
22 be taken - because we've all been really

1 critical, and need to be taken in that context  
2 that we really want - I think these documents  
3 tend to take on a life of their own after they  
4 get finalized. And in the spirit of making it  
5 the best document possible, I think that's  
6 what we're trying to do.

7 But I think speaking as an  
8 epidemiologist, I'm really happy to see that  
9 human studies are going to be considered with  
10 all their faults and limitations and so forth.  
11 But I do want to expand on one other point  
12 that - it's actually two points that have a  
13 similar sort of conclusion.

14 When we try and include - it's  
15 almost impossible to include a totally  
16 representative sample in our study, but the  
17 goal of representativeness is so you can  
18 generalize the findings to a larger  
19 population.

20 And this ties into a different  
21 point which was made earlier about  
22 distinguishing confounding from effect



1 modification, and I specifically want to  
2 address effect modification in terms of  
3 susceptible populations.

4 So, as epidemiologic studies are  
5 considered, and they're considered in terms of  
6 their generalizability, I think they also need  
7 to be considered in terms of whether they are  
8 representing subgroups of a population that  
9 might be at high risk.

10 So, the example of the AHS is a  
11 good one in this regard. I think it's a  
12 fantastic study. It's going to answer a lot  
13 of questions. However, it's based in two  
14 states that are relatively homogenous. I said  
15 relatively, not completely.

16 But I think other studies need to  
17 be considered in terms of could you expand  
18 what you know about susceptible populations.  
19 And, again, using the existing cohorts or  
20 developing new ones, even, ought to be  
21 considered.

22 So, I think the point of effect

1    modification feeds into this generalizability  
2    issue a bit.  If you want to examine studies  
3    that you can generalize to wider populations  
4    and look at susceptible subgroups, then  
5    additional populations need to be included in  
6    some of these studies.

7                    CHAIR HEERINGA: Steve Heeringa.

8    And just to follow up on Dr. Reif's comments  
9    in teaching these subjects to many graduate  
10   students who are going to be dealing with  
11   these issues, this whole issue of confounding,  
12   moderation and mediation, terms that are kind  
13   of, the latter two, increasingly creeping into  
14   the literature, I think it would be very good  
15   to delineate specifically in this paper what  
16   we're referring to there, because people  
17   scramble those things up and they're very,  
18   very different.

19                   And so I think it's a fairly small  
20   enhancement to this, but to make that clear  
21   from the beginning so we don't sort of just  
22   lapse into the use of the term "confounding"

1 for things that are actually mediating effects  
2 and proxying them.

3 Dr. Bailar.

4 DR. BAILAR: I'd like to offer a  
5 rule of thumb. I don't know if it's even  
6 precise enough to find a place in this  
7 document, but it's something to think about.

8 After a lot of years looking at a  
9 lot of studies, it seems to me that almost  
10 always if adjustment with a first group of  
11 confounders doesn't make much difference, then  
12 adjustment with more confounders and better  
13 data on the confounders is not likely to make  
14 any difference as well.

15 If your first rough adjustment  
16 makes a substantial difference, then getting  
17 more data and more confounders is likely to  
18 make a further change in your estimate in the  
19 same direction.

20 That might be a way to sort of  
21 sort out where you want to put your next  
22 efforts. Focus on the ones where it looks

1 like there's really something going on with  
2 the confounders.

3 CHAIR HEERINGA: Dr. Bove.

4 DR. BOVE: I'll just say one more  
5 thing. I agree with Ellen and I really  
6 appreciate the EPA is emphasizing  
7 epidemiologic studies in risk assessment. And  
8 I think examples of where they've been used in  
9 other areas like, for example, the TC risk  
10 assessment, the dioxin risk assessment, were  
11 really helpful.

12 But I guess I also feel that it  
13 would be good to have the same critical  
14 approach to the tox literature and tox  
15 research as you seem to have with epi  
16 research. This is just a thing I have because  
17 I have to deal with it at my own agency over  
18 and over again, toxicologists interpreting epi  
19 studies, but usually not the other way around,  
20 epidemiologists interpreting tox studies.

21 And it would be good for  
22 epidemiologists to interpret epidemiologic

1 studies, because I think they can better  
2 evaluate those studies than toxicologists, and  
3 vice-versa. I think toxicologists often do a  
4 better job of evaluating their own research  
5 than epidemiologists do. At least that's how  
6 it is in my agency.

7 CHAIR HEERINGA: Okay. I think  
8 what I'd like to do at this point, is to call  
9 a break for 20 minutes, and we'll reconvene at  
10 10:20. And at that point - oh, Dr. Lowit.

11 DR. LOWIT: I'd just like to make  
12 one point that loud and clear we hear that a  
13 certain section needs a major rewrite.

14 To the extent that many of you, if  
15 not all of you, had a lot of very specific  
16 points, I mean if this is a long response or  
17 even a very bulleted list of all the things,  
18 I mean every detail that came up today was,  
19 you know, I gave up with the notes a long time  
20 ago.

21 CHAIR HEERINGA: Right. You  
22 shouldn't have to do that.

1 DR. LOWIT: So, if the report can  
2 be very detailed and very specific, that would  
3 be helpful.

4 CHAIR HEERINGA: I think that you  
5 can assume that that will be the case. And I  
6 think as Dr. Bove started his comments out, he  
7 didn't want to provide every last comment, but  
8 we will provide those bulleted. And if it  
9 gets down to Line 5 punctuation, we'll give  
10 you that too in the appendix, but we won't do  
11 that here.

12 And so, yes, rest assured that we  
13 will do that so that you get not only the  
14 general guidance, but also specific guidance.

15 DR. LOWIT: And a couple of  
16 individuals, including yourself, suggested  
17 specific places where definitions need  
18 clarification or there's some specific nuance  
19 that you felt that was important, and really  
20 make sure that those points are also -

21 CHAIR HEERINGA: We'll give  
22 citations, too, to help with that. Dr.

1 Portier is capturing that.

2 Okay. Let's take a 20-minute  
3 break, and we will return and move on to Part  
4 1.2.

5 And, again, for the panel and for  
6 EPA staff if there are other questions or  
7 other comments that occur to people as we move  
8 through this on 1.1, we will have a chance to  
9 return to everything at the end, too.

10 (Whereupon, the above-entitled  
11 matter went off the record at 10:03 a.m. and  
12 resumed at 10:22 a.m.)

13 CHAIR HEERINGA: Okay. Welcome  
14 back, everyone, to the second of the morning  
15 session of our second day of the meeting of  
16 the FIFRA Science Advisory Panel.

17 We have completed the panel's  
18 initial discussion of Charge Question 1.1, and  
19 we're turning to Charge Question 1.2 if Dr.  
20 Lowit can find her controller.

21 Jeff Dawson will read Question 1.2  
22 into the record.

1                   MR. DAWSON: Question 1.2. Section  
2    III of the draft framework describes the major  
3    sources of human incident data along with  
4    their strengths and limitations. Section III  
5    also describes ways to use human incident data  
6    in risk assessment. Please comment on the  
7    soundness and completeness of these  
8    discussions. Please include comments on  
9    additional factors to consider when evaluating  
10   the quality and weighing the utility of human  
11   incident data in risk assessment and  
12   characterization.

13                  CHAIR HEERINGA: Our lead  
14   discussant is Dr. Chambers. Jan.

15                  DR. CHAMBERS: Well, this had to be  
16   quite a challenge to deal with these isolated  
17   incidents.

18                  Incident reports are usually high  
19   dose, frequently illegal or accidental  
20   exposure incidents. So, they would not be  
21   reflective of normal use exposures.

22                  The several sources of incident



1 data are varied substantially in their  
2 completeness, level of description and  
3 geographic scope. And in my opinion, EPA has  
4 evaluated the utility and reliability of these  
5 five sources well, and seems to have made an  
6 adequate judgment of the value and usefulness  
7 of these sources.

8           Since the incident data are  
9 frequently of limited detail and are largely  
10 the observations of non-medically trained  
11 individuals, these data are of relatively  
12 limited usefulness.

13           The observations in incident  
14 reports are usually short term with only a  
15 little amount of follow-up of incidents  
16 available. Especially when the risk  
17 assessments need to be made on longer term  
18 adverse effects, the incident data are  
19 probably of relatively little value because I  
20 think your regulatory processes have pretty  
21 much protected people, ag workers and so  
22 forth, from the high-dose, short-term effects.

1                   Exposure estimates in these cases  
2   are probably very limited quantitatively and  
3   of limited reliability. In addition, the  
4   incidents are reported on products, not single  
5   compounds. So, the possible interactions or  
6   synergies of the main active ingredient with  
7   other chemicals are unknown.

8                   In addition, there's probably  
9   little, if any, information available in  
10   incident reports to indicate what other  
11   factors or confounders, and I'm not sure I've  
12   used that term correctly now, but what other  
13   factors might have been present that might  
14   have contributed to the symptoms reported.

15                  Therefore the incident reports, in  
16   my opinion, are of very limited value to the  
17   risk assessment process.

18                  A special concern to me, anyway,  
19   is the report of symptoms by medically  
20   untrained individuals. Such descriptions of  
21   symptoms may be highly problematic and that  
22   those reporting on the incident may not be

1 attune to the types of observations that  
2 should be made.

3           When an incident occurs that is an  
4 accident and it's potentially high dose, it  
5 would seem very likely that the affected  
6 individual would be very scared, in my  
7 experience, and report signs and symptoms that  
8 are more physiological reactions to fright  
9 than to the mechanistic effects of the  
10 chemical.

11           Caution is urged and the  
12 conclusions drawn on symptoms that could be  
13 attributed to physiologic stress reactions if  
14 those are not consistent with the plausible  
15 toxicological effects for a chemical.

16           Also, classic flu-like symptoms  
17 are frequently cited as an adverse acute  
18 consequence of exposure to some pesticides,  
19 and those could also be attributed to some  
20 non-chemically induced causes.

21           The uses cited for incident data,  
22 that is the need for changes in risk

1 management, monitoring success in mitigation  
2 measures, targeting enforcement activities,  
3 are all reasonable uses of the incident data  
4 assuming that the incident data are carefully  
5 critiqued for reliability.

6 This is probably their greatest  
7 value in the overall risk management process  
8 since these typically high, accidental off-  
9 label occurrences are of relatively little  
10 value in the risk assessment process.

11 CHAIR HEERINGA: Thank you, Dr.  
12 Chambers.

13 Dr. Reed.

14 DR. REED: In terms of coverage in  
15 this section, the coverage on the five  
16 databases and their brief description, I  
17 think, is sufficient for presenting their main  
18 characteristics in the context of their  
19 usefulness or not for risk assessment. And I  
20 find Table 3 very useful as a summary.

21 The description of this section  
22 present the toxicity data tally, seem to be

1 focusing on the severity ranking. And I think  
2 it's not until the diazinon example that the  
3 end points, the importance of end points came  
4 out.

5           And I think it would be good to  
6 bring that to the front because as a risk  
7 assessor, we would look at it and we're  
8 interested in the most sensitive end point.  
9 And that turned out to be the lowest ranking  
10 in terms of severity, and so it didn't come  
11 out until later.

12           You can either just point the  
13 reader to that section and, you know, not to  
14 explain too much on this.

15           The other thing, and I think it  
16 was mentioned with the epi study in the same  
17 way, that it's good to just point out the  
18 importance of looking at human data in the  
19 context of what's known about or not about  
20 mode-of-action. So, you get a sense of how it  
21 fits in into the entire risk assessment  
22 process. And mode-of-action, including all

1 the related in vitro data. I think there's in  
2 vitro data that comes into play to line all  
3 the information up.

4           There's a couple places where it  
5 was mentioned that the data collecting  
6 agencies defend their separate data analysis,  
7 but I think it would be good to put an example  
8 of what kind of analysis that they did and  
9 what kind of conclusion they come up with.  
10 Sort of get a sense of how other people use  
11 these databases. And of course it would be  
12 most interesting if it's related to pesticide  
13 exposure and risk.

14           In terms of California data, the  
15 PISP, and I have not done that personally, but  
16 I always wonder - we're talking about the lack  
17 of information in the incidents report. And  
18 I was wondering if the agency could look into  
19 pulling in the used data to take a look at the  
20 incidents report and see if you can get more  
21 confirmation/information out of the used  
22 report in terms of what they were exposed to

1 and that kind of stuff.

2 As a risk assessor, this is great.  
3 I mean we're looking at human data. But as a  
4 risk assessor when I was looking at how to use  
5 incidents data, I cannot help but to thinking  
6 that if I get a good job, my job is right and  
7 risk assessment being predictive, then you're  
8 not going to see much of the incidents except  
9 for accidental and misuse and intentional.

10 So, from that standpoint, I am  
11 looking at incidents data not just as a group,  
12 but I think I get the gist that we're looking  
13 at incidents data like the way we look at epi  
14 data, which is not, and it's not.

15 So, I'm more interested in  
16 actually picking through the incidents data.  
17 I know a majority of them there's no follow  
18 through and with all the deficiencies that Dr.  
19 Chambers had mentioned. But there might be a  
20 few data sets that you can follow up a little  
21 bit to see if there's enough information to  
22 bring it into consideration in risk

1 assessment, so that you could maybe glean from  
2 it either how to modify, how to improve, how  
3 to - or to confirm the certainty or  
4 uncertainty of risk assessment.

5 And, again, I'm coming from the  
6 standpoint of hopefully these are not to  
7 happen. But if it happens, I'm all perked up.  
8 I want to know what happens to these cases  
9 where there's enough follow-up.

10 So, It's not necessarily confining  
11 ourselves in looking at the incidents data as  
12 a whole, as a whole group, but possibly  
13 gleaning something out of it that could be  
14 useful for risk assessment, sensitive  
15 subpopulation, vulnerable population, that  
16 kind of information.

17 CHAIR HEERINGA: Thank you, Ruby.

18 Dr. Gold.

19 DR. GOLD: Well, I want to say I  
20 agree with virtually everything Dr. Chambers  
21 said, but I do have a few things to add just  
22 in terms of considerations that might be



1 included in the document in terms of the  
2 utility of these reporting systems.

3 So, one thing in terms of  
4 reporting systems in general is if this is  
5 mandatory or voluntary. And if it's  
6 mandatory, who's required to report, because  
7 who reports also affects the under-reporting.

8 So, I mean what we're concerned  
9 about, one concern that comes up in using  
10 these systems is the under-reporting, and  
11 that's affected by a lot of things. Is it  
12 mandatory or is it voluntary?

13 Also, is there sort of active  
14 reporting or passive reporting? In other  
15 words, does the agency actually actively go  
16 out and seek these reports or do they just  
17 passively wait for physicians or whoever,  
18 registrants or whatever to report? This will  
19 affect under-reporting as well.

20 And in terms of how the data can  
21 be used for trends over time and so forth, I  
22 think in terms of weighting the utility, so

1    how useful it is, I think, is how much it's  
2    tied to - how much the incident reporting is  
3    tied to pesticide use over time, for example,  
4    because it could be that you have increased  
5    incidents for lots of reasons.

6                It could be increased usage, it  
7    could be better reporting for one reason or  
8    another, it could be the population has  
9    increased, it could be a sensitive population.  
10   There are lots of reasons.

11               And so to the extent that you can  
12   link these data with other pieces of  
13   information like that, I think you have the  
14   potential for increasing the utility. But I  
15   think it's significantly limited, as Dr.  
16   Chambers indicated.

17               CHAIR HEERINGA: Thank you, Dr.  
18   Gold.

19               Dr. Meek.

20               DR. MEEK: I don't have very much  
21   to add. I just wanted to mention that in fact  
22   the human incident data, it can be used in

1 risk assessment to a limited extent. The  
2 human case reports and surveillance of acute  
3 poisonings are quite helpful in considering  
4 similarities in site concordance between  
5 animals and human in mode-of-action analysis.

6 So, the concordance table that Dr.  
7 Lowit showed yesterday, in fact that  
8 information has a place in a qualitative  
9 context in terms of looking at site  
10 concordance. So, I would suggest that the use  
11 of these data really isn't restricted to  
12 hazard identification as indicated, but they  
13 also play a role in hazard characterization.

14 So, I think that's all I would  
15 add.

16 CHAIR HEERINGA: Thank you, Dr.  
17 Lowit. Other members of the panel?

18 Dr. Bailar?

19 DR. BAILAR: I'd like to add just  
20 one point. I do not recall that there was  
21 anything in this draft document that dealt  
22 with reports of clusters.

1           Three pesticide applicators who  
2 happen to work in the same field at different  
3 times come up with brain cancer. 17 workers  
4 in a pesticide plant had kidney failure when  
5 population rates would suggest there shouldn't  
6 be more than five.

7           I think it would be worth adding a  
8 paragraph or two about these. Cluster reports  
9 are notoriously difficult to interpret, and  
10 you might just say something like that. The  
11 problems of reporting bias, a cluster doesn't  
12 come to attention unless it's outstanding.  
13 You never hear about all the places where that  
14 didn't happen.

15           Just as a sideline, I remember  
16 many years ago I saw a report of a particular  
17 complication with a blood transfusion in a  
18 hospital. Somebody calculated the probability  
19 of that was one in 7,000.

20           What struck me at the time was  
21 that I happen to know there are about 7,000  
22 general hospitals in the U.S. None of the

1 others ever reported this. They declined it.

2 So, the one in 7,000 event  
3 probably occurred with exactly the expected  
4 frequency. The one in a million event does  
5 occur with the expected frequency.

6 So, you might want to add  
7 something about clusters.

8 CHAIR HEERINGA: Dr. Chambers.

9 DR. CHAMBERS: I guess you mean  
10 clusters with respect to epi or with  
11 incidents?

12 DR. BAILAR: I'm talking about  
13 clusters that are reported probably through  
14 the incidents mechanism, but where you're not  
15 dealing with an individual, a report on an  
16 individual, but rather a report on a group of  
17 people who have something in common like an  
18 exposure.

19 DR. CHAMBERS: But my understanding  
20 of these is that it is on individuals that are  
21 showing up in Poison Control Center records  
22 and that sort of thing on some particular

1 exposure -

2 DR. BAILAR: Well, what should EPA  
3 do if they find a report of a cluster? This  
4 falls - in my view, this falls in sort of the  
5 same category as incident reports.

6 DR. CHAMBERS: It wouldn't be - I  
7 don't think it would be the same database  
8 though, would it? It would show up in some  
9 other way.

10 DR. MANIBUSAN: So, just to  
11 clarify, if there are multiple cases of  
12 adverse events from the same area, that could  
13 show up in our IDS system, which is a  
14 voluntary system. It's mandatory for  
15 registrants to submit that information to us,  
16 but it's voluntary in the sense of the person  
17 who's reporting it to the registrant.

18 DR. CHAMBERS: Would it be  
19 something as the example that Dr. Bailar used  
20 as brain cancer or something like that? These  
21 are more acute reports, aren't they?

22 DR. MANIBUSAN: Right. So, the

1 incident information that we often get is more  
2 from acute exposure, acute symptomology, not  
3 on chronic affects like brain tumors or  
4 chronic toxicity.

5 DR. HEERINGA: Dr. Harris.

6 Dr. Harris: Shelley Harris. Maybe  
7 I'll just jump in here. We just need to make  
8 a distinction between clusters or poisonings  
9 and clusters of cancer. And typically if  
10 you'd have a cancer cluster, someone would  
11 call your local health department and they  
12 would call the various agencies involved and  
13 ask for an investigation.

14 So, I think that cluster  
15 investigations might be more appropriately  
16 included in the overview of epidemiologic  
17 studies in the first question and more fully  
18 described in that area.

19 CHAIR HEERINGA: Dr. Lowit, and  
20 then I'll come back.

21 DR. LOWIT: Just to add a point to  
22 add to what Mary said to clarify, there have

1    been situations where we have in the past,  
2    where we have seen clusters where there are  
3    acute events.  There's an aldicarb in  
4    watermelon example.  And there was a field  
5    example with some female workers who had  
6    reported birth defects, I can't remember the  
7    chemical, from a few years ago.

8                So, there have been clusters of  
9    events, some of which you may have picked up  
10   in an incident because of an acute event,  
11   let's say, from a carbamic, for example, but  
12   then there's maybe some intermediate term end  
13   points, but then obviously if you have a  
14   cancer cluster.

15               So, it fits across different modes  
16   of action by duration.

17               CHAIR HEERINGA: Dr. Portier.

18               DR. PORTIER: Actually, this  
19   discussion is good.  And recently I was  
20   looking at California's cancer cluster plans,  
21   and cancer clusters are handled really well.  
22   It's these more acute things.



1                   What I wanted to do is get back to  
2 Dr. Gold's issue about vulnerable populations.  
3 So, when you're analyzing these things, what  
4 if you notice that the people who are calling  
5 in who are having these effects are all field  
6 workers, minority, you know, kind of the  
7 vulnerable, unprotected class?

8                   I mean is there discussion in  
9 there about identifying vulnerable  
10 populations, which is another part of hazard  
11 identification, right, and finding those.

12                  So, that's not geographical  
13 clusters, per se. That's more demographic  
14 clusters or demographic ID or something of  
15 that type.

16                  CHAIR HEERINGA: There was a  
17 question, so I'll -

18                  DR. MANIBUSAN: Let me try to take  
19 a stab at answering that. We have not yet  
20 started to look at using incident data for  
21 environmental justice issues. We've tried to  
22 do that.

1                   We have some limitations, of  
2   course, because many of these databases do not  
3   include things like zip codes where we can  
4   easily query.

5                   We have to the extent that the  
6   data is available to us, looked at the  
7   differences between adult versus children's  
8   adverse reporting of cases.

9                   And in situations where we notice  
10   that children are predominantly reporting  
11   adverse symptoms either because they have  
12   direct access to the product, we can do things  
13   to reduce that risk in terms of special  
14   packaging, things like that that we've done in  
15   the past with incident information.

16                  CHAIR HEERINGA: Jeff Dawson.

17                  MR. DAWSON: Just another example  
18   to follow on with what Mary said in the risk  
19   management area related to workers.  
20   Historically we've seen clusters of incidents  
21   related to, for example, field workers going  
22   in too early to harvest certain crops and

1 certain chemicals. So, right away that would  
2 be kind of a red flag for us to kind of alter  
3 the risk management approach for that. And  
4 there have been notable examples over time  
5 with that.

6 CHAIR HEERINGA: Dr. Reed.

7 DR. REED: Jeff, when I mentioned  
8 vulnerable and sensitive subpopulations, age  
9 was one other thing. There's greater  
10 frequency of showing up in incidents report  
11 with children.

12 But also vulnerable people may be  
13 an applicator or a group of people that could  
14 be used to both, again, as indicated, go back  
15 and look at the exposure assessment, look at  
16 the risk assessment, different components of  
17 risk assessment.

18 But also in terms of risk  
19 management, you can cater your education,  
20 information, dissemination of a group of  
21 people who have a tendency, you know, greater  
22 tendency to not using the pesticide right or

1 even not being able to read the label right  
2 because of ounce, gallon, units like that.

3 So, that's what I'm thinking of  
4 when I say vulnerable sensitivity.

5 CHAIR HEERINGA: Dr. Gold.

6 DR. GOLD: I want to address Dr.  
7 Bailer's point. I think clusters are -  
8 they're really difficult, but I think what he  
9 is suggesting is that they get mentioned  
10 somewhere. And whether it's here or in the  
11 epidemiology section, I don't think it  
12 matters.

13 But I think part of what I have a  
14 little trouble about is you're talking about  
15 clusters that show up in your reports to these  
16 various agencies, and out in California we  
17 have clusters all the time and often they're  
18 not linked to anything in particular.

19 Often we just hear that there's a  
20 cluster of birth defects or clusters of asthma  
21 or clusters of this or that. And people will  
22 say well, we think it's the pesticides that

1 are in the fields adjacent. It's a non-  
2 specific. So, it's not related to a  
3 particular product or agent.

4 And so I think adding a paragraph  
5 or two about things like this because they do  
6 occur, and how you should handle them and with  
7 great skepticism and care, but it is something  
8 that the public is concerned about.

9 So, I think not mentioning it is  
10 somewhat of an omission. And so mentioning it  
11 delicately and properly and not always  
12 oriented to a particular product. Okay?  
13 Because that's not how they always occur.

14 I mean sometimes the community is  
15 just concerned and they just see a lot of  
16 something, and they're not relating it to a  
17 specific agent in particular.

18 CHAIR HEERINGA: There's a nice  
19 paper, and I believe it's by Persi Diaconis,  
20 on this whole issue of how humans sort of  
21 over-interpret clustering of events when in  
22 fact - the randomness of those cluster

1 occurrences. And I'll try to throw that  
2 citation in. It's pretty accessible because  
3 I think it was published in Scientific  
4 American or something like that.

5 So, it's just a citation to throw  
6 in there on this whole issue of how to address  
7 clustering.

8 Dr. Reif.

9 DR. REIF: Yes. There's also an  
10 issue of the American Journal of Epidemiology  
11 in 1992 that devoted a whole issue to analysis  
12 of clusters and cluster busters, and that also  
13 would be a useful reference.

14 CHAIR HEERINGA: Dr. Bove.

15 DR. BOVE: Let me just say one  
16 thing about clusters. First of all in this  
17 database, you will be able to link particular  
18 products with the cluster. So, actually this  
19 is a little different than the usual  
20 circumstance where people say there's a lot of  
21 cancer on my block and we're not sure what's  
22 around.

1 But there have been cluster  
2 investigations that have ended up into full-  
3 fledged epi studies, Woburn, for example,  
4 using very sophisticated water modeling to  
5 determine exposure.

6 So, cluster investigations can  
7 move towards a full-fledged epi study and that  
8 needs to be - that will be mentioned in that.

9 CHAIR HEERINGA: Okay. Mary.

10 DR. MANIBUSAN: I just want to ask  
11 maybe for some clarification, it sounds like  
12 there is a recommendation for us to do more  
13 active surveillance. So, realtime  
14 information.

15 Right now we don't currently have  
16 access to realtime incident data inputting, so  
17 we purchase PCC data, for example, in two-year  
18 increments, and there's a lag of about three  
19 years for data quality. Our incident data  
20 from our registrants are submitted perhaps  
21 quarterly. It's not on a day-to-day basis.  
22 We don't have that active surveillance system.

1                   And I think there are articulated  
2   very clearly right now, our incident  
3   information is reported to the agency in paper  
4   copies.

5                   CHAIR HEERINGA: The question -

6                   DR. MANIBUSAN: So, some  
7   suggestions about that.

8                   CHAIR HEERINGA: The question to  
9   the panel, I think, is should this be done or  
10   not. I would add is it feasible both in terms  
11   of its timeliness and the cost that it would  
12   take for the benefit that's reaped.

13                  Dr. Bailar.

14                  DR. BAILAR: I was not meaning to  
15   suggest that there should be any expansion of  
16   that particular effort. I think you should  
17   continue doing what you're doing. It's  
18   potentially useful. You will certainly come  
19   under criticism if you don't do it, but I  
20   wouldn't look to that for big answers to big  
21   questions.

22                  CHAIR HEERINGA: Other thoughts on



1 that particular issue? Hopefully that  
2 clarifies. I think there seems to be  
3 consensus.

4 Yes, Dr. Hayton.

5 DR. HAYTON: Well, this discussion  
6 makes me think about the fact that the  
7 systemic exposure to a chemical is not only  
8 the external exposure, the applied dose, but  
9 also the clearance of the chemical.

10 And that when you talk about  
11 susceptible populations, people who are  
12 missing the gene that makes the enzyme that  
13 metabolizes, say, the chemical, how do you -  
14 I don't know what the answer is, but how do  
15 you pick that up? And it's sort of a  
16 characteristic of the population looking for  
17 sensitive individuals.

18 For example, cytochrome P450 2D6  
19 is a classic example. And if you're using a  
20 drug in therapy and somebody is a poor  
21 metabolizer, about ten percent of Caucasians  
22 I think is how it works, are deficient in that

1 enzyme, then - in therapeutics, we're trying  
2 to identify those people beforehand and adjust  
3 the dose accordingly.

4 But is there a role in monitoring  
5 for that?

6 DR. MANIBUSAN: Right. Now, you  
7 bring up a very good point.

8 I think it's very challenging to  
9 think that we can use incident data to  
10 identify susceptible populations on molecular  
11 basis.

12 I think it calls back to the  
13 framework analysis. The framework really  
14 provides an opportunity to integrate what we  
15 know about a chemical through its mode-of-  
16 action, through its human relevancy. We can  
17 make some determinations about what we're  
18 seeing in the animal and how relevant it is to  
19 humans.

20 In our risk assessment, our risk  
21 assessors around the table, we have  
22 uncertainty factors to account for some

1 variability that we might not be able to  
2 anticipate in our end points that we're seeing  
3 in our animal studies.

4 We have an intra species  
5 uncertainty factor to account for that, but it  
6 is a very big challenge for risk assessment to  
7 try to identify sensitive subpopulations with  
8 differences in CYP induction, with differences  
9 in metabolism.

10 CHAIR HEERINGA: Thank you, Dr.  
11 Manibusan.

12 Dr. Bailar.

13 DR. BAILAR: Dr. Hayton mentioned  
14 the deactivation genes. There also should be  
15 some concern about activation genes with this  
16 vinyl chloride and some other things. And  
17 it's worth noting that each of those bends the  
18 dose response curve in opposite directions,  
19 but their source is non-linearity, which might  
20 be important.

21 CHAIR HEERINGA: Dr. Chambers.

22 DR. CHAMBERS: I think both those

1 points are very important. But this question  
2 is about incident data, and I don't think  
3 you're going to get anywhere near enough  
4 information to make any judgments about that.  
5 Perhaps not in some epidemiological type  
6 studies.

7 But with respect to this  
8 particular question, I don't think you're  
9 going to get information like that.

10 I would have to question how much  
11 - you're going to have to do a time benefit  
12 analysis. Certainly I know you're stretched  
13 to the limit on an awful lot of activities and  
14 whether or not putting a lot more effort into  
15 this activity is going to get you information  
16 that's of value where you could put energy  
17 into other activities, you're going to have to  
18 make that judgment.

19 CHAIR HEERINGA: Okay. Dr.  
20 Manibusan, Dr. Lowit?

21 Let's move on then to Part 1.3.

22 DR. LOWIT: Section IV of the draft

1 framework describes a proposed WOE approach  
2 for evaluating human and experimental animal  
3 data from in vitro and in vivo studies. This  
4 proposed approach makes use of the "source to  
5 outcome pathway" and the modified Bradford  
6 Hill criteria like that in the MOA Framework,  
7 as tools for organizing, evaluating and  
8 describing the human health consequence of a  
9 particular chemical based on available data.  
10 Please comment on the proposed use of the  
11 modified Hill criteria in the context of the  
12 source to adverse outcome pathway for  
13 integrating a variety of types of data at  
14 different levels of biological organization  
15 including human incident and epidemiologic  
16 data in risk assessment.

17 CHAIR HEERINGA: And Dr. Meek is  
18 the lead discussant here, and I think also for  
19 1.4.

20 DR. MEEK: Right. They're a bit  
21 similar, 1.3 and 1.4, so we may cover most of  
22 it currently.

1 CHAIR HEERINGA: We'll just stick  
2 with 1.3 and -

3 DR. MEEK: Okay. Well, in my view,  
4 use of the source to adverse outcome pathway  
5 and the modified Bradford Hill criteria is  
6 extremely helpful not only as a basis for  
7 organizing, evaluating, describing the human  
8 health consequence of a particular chemical  
9 based on the available data, but also in  
10 identifying critical data gaps.

11 And so I really think that the  
12 agency is to be commended on their pioneering  
13 work on the framework, its contribution to  
14 transparency and risk assessment generally and  
15 I really am very supportive.

16 I also think that thinking in this  
17 context is important in transitioning our  
18 focus in toxicology and risk assessment from  
19 delayed adverse effects that we normally  
20 consider to earlier biomarkers of exposure and  
21 effect so as to collect more informative human  
22 data at relevant dose levels. So I think it,

1 again, it serves really a dual purpose.

2           The framework is also helpful in  
3 directing attention very early in the  
4 assessment available data to dose-response  
5 relationships for early key events, and it is  
6 these dose-response relationships that are  
7 critical in the subsequent risk  
8 characterization.

9           So, I believe that the source to  
10 adverse effect pathway and framework offer  
11 significant potential that transparently and  
12 appropriately integrate human and  
13 toxicological data as proposed in the  
14 documentation.

15           That said, and there's always a  
16 but, in my view, however, there is clear  
17 benefit to be gained in more clearly  
18 distinguishing the qualitative and  
19 quantitative aspects of mode-of-action  
20 analysis and human relevance as a basis for  
21 integration of human data and subsequent dose-  
22 response characterization.

1                   While preexisting epidemiological  
2   and incident reporting can be helpful in  
3   hazard characterization, unless we're able to  
4   robustly access exposure or more appropriately  
5   incorporate biomarkers of exposure and effect  
6   based on identification of key events in a  
7   mode-of-action context, the contribution to  
8   dose-response characterization will  
9   necessarily be more limited.

10                  I think that's very nicely  
11   characterized in the source documentation in  
12   Figure 1. And so the kinds of data that we're  
13   looking for in an epidemiological context are  
14   pretty clearly highlighted there.

15                  I also think that consideration of  
16   the human and toxicological data and the  
17   context of the framework contribute to  
18   conservation of resources. For example, lack  
19   of adequate characterization of exposure-  
20   response relationships in epidemiological  
21   studies may preclude the need to do an  
22   extensive weight of evidence analysis for



1 these data since they cannot contribute to the  
2 risk characterization.

3           So, you would actually have to  
4 change the order of the way that you look at  
5 different types of data. And I think I'll  
6 come back to that at the end of my comments,  
7 because in large measure I think this relates  
8 to how you might meaningfully use problem  
9 formulation.

10           So, another point I want to make,  
11 the value of framework analysis and  
12 coordinating assessment in research has not  
13 been emphasized in the documentation.

14           For example, there is repeated  
15 reference to problem formulation, but without  
16 indication of how the broader toxicological  
17 and epidemiological databases might be  
18 considered at this stage in integrated fashion  
19 as a basis to identify critical data gaps to  
20 inform the assessment.

21           This would be the appropriate step  
22 in my view, for example, to identify

1 limitations in available human data in the  
2 context of the overall database, as a basis  
3 either to focus additional research or at  
4 least to increase understanding of the likely  
5 contribution of the existing human data in the  
6 context of the overall database, and that's  
7 critical.

8           The appropriate human data might  
9 include in vitro studies in human tissues or  
10 cell lines and perhaps very focused  
11 epidemiological studies to address the  
12 specific questions and identified subgroups  
13 through consideration of early biomarkers of  
14 effect.

15           A couple of points as well, these  
16 are more specific about the criteria used in  
17 the framework specifically, it's important to  
18 recognize that the criteria used in the  
19 framework here are those that relate  
20 principally to weight of evidence rather than  
21 consideration of individual studies. And  
22 that's the difference between the Bradford

1 Hill criteria as applied to the consideration  
2 of causality and epidemiological studies and  
3 their consideration in this framework.

4 And that's appropriate, because  
5 what you're doing is looking at the weight of  
6 evidence.

7 Based on increasing experience and  
8 application of the mode-of-action human  
9 relevance framework and to avoid confusion  
10 that this addresses exposure in any way, it's  
11 suggested to consider revising reference to  
12 dose-response relationships to concordance of  
13 dose-response relationships between the key  
14 and end events. It's not just that there's a  
15 dose-response relationship.

16 I also think that there's  
17 confusion with exposure, which is considered  
18 in a different part of the risk assessment  
19 paradigm. So, I think it's very important to  
20 be explicit in describing what we're actually  
21 doing in that step.

22 Also, we don't expect here to have

1 earlier key events occurring at lower doses  
2 where the data don't support the hypothesized  
3 mode-of-action. The document was not very  
4 clear on that point.

5 We also expect the incidents of  
6 earlier key events to be greater than or equal  
7 to that for the end toxic effect where the  
8 weight of evidence doesn't support the  
9 hypothesized mode-of-action either. So, those  
10 are more specific points to the actual  
11 documentation.

12 Another point is based on  
13 increasing experience with the mode-of-action  
14 human relevance framework, I think we would  
15 normally consider potential alternatives for  
16 hypothesized modes of action at the outset of  
17 a framework analysis as a basis to distinguish  
18 relevant pathways and key events in an  
19 integrated fashion. So, I think it was just  
20 something to take into consideration.

21 So, I have a number of more  
22 specific comments as well to the

1 documentation, but I won't present them here  
2 because there's probably no need to.

3 CHAIR HEERINGA: Thank you, Dr.  
4 Meek.

5 Dr. Hayton.

6 DR. HAYTON: Yes, I agree with Dr.  
7 Meek. I thought the Bradford Hill criteria  
8 were highly appropriate and they're well  
9 accepted. And since I don't have a lot of  
10 expertise in epidemiology anyway, I didn't  
11 want to say other than it made sense to me.

12 One comment that resonated with me  
13 is that the criteria shouldn't be viewed as a  
14 checklist, but rather just as a group of  
15 characteristics that taken together provide a  
16 systematic way to aggregate observations.

17 And then an issue that came up  
18 yesterday that not all the criteria deserve  
19 equal weight, I think there's something to  
20 that. So, weighting among the criteria would  
21 be an issue.

22 In Section IV, I didn't see very

1 much about extrapolation of dose amongst  
2 species and extrapolation of high-dose  
3 toxicity in experimental animals and human  
4 incident cases to environmental exposure. In  
5 humans, it typically occurs at much lower  
6 doses, and I'm just wondering how the  
7 extrapolation would be done.

8           Would it be a linear, low-dose  
9 extrapolation would be the standard approach,  
10 or other approaches and issues surrounding the  
11 phenomenon known as hormesis where low doses  
12 actually seemed to provide a protective  
13 effect, and it just occurred to me that some  
14 thought ought to be given to including that  
15 issue in the framework.

16           And maybe it has and maybe you  
17 decided just not to put it in, but that's what  
18 stuck out to me.

19           CHAIR HEERINGA: Thank you, Dr.  
20 Hayton. I think the point that you raise has  
21 been a point of considerable debate and also  
22 a guideline formation within the agency.

1 Dr. Bucher.

2 DR. BUCHER: John Bucher. So, the  
3 draft framework for integration of in vitro/in  
4 vivo animal and human incident in epidemiology  
5 studies has many advantages and the agency  
6 should be congratulated for their efforts.  
7 There's really no question that establishing  
8 steps to ensure rigorous and consistent  
9 evaluation of studies of any type result in a  
10 better risk assessment.

11 The mode-of-action framework  
12 certainly helps in the organization and  
13 evaluation of the data. That said, it's  
14 important to remember the historical context  
15 and purposes for developing the MOA  
16 frameworks. These originally focused on  
17 cancer outcomes, and only more recently have  
18 been extended to non-cancer end points.

19 For decades, positive findings  
20 from animal cancer studies were assumed to be  
21 relevant for human hazard identification. In  
22 the late '70s and early '80s, research

1 programs were begun to systematically examine  
2 the biological events that appeared to  
3 correlate with and perhaps account for the  
4 induction of cancer and the number of common  
5 sites for tumor responses in rodent cancer  
6 studies.

7           The original mode-of-action  
8 framework for experimental animal tumor sites  
9 and types was established to ensure that the  
10 many modes of action hypotheses were being  
11 offered up to, frankly, explain away  
12 problematic results were in fact based on  
13 solid, scientific foundation.

14           The second mode-of-action  
15 framework, which is Bette's framework,  
16 affectionately known as Bette's framework, was  
17 established to specifically examine the claims  
18 that certain animal tumor mode-of-actions were  
19 in fact not relevant for humans.

20           And this proved to be an  
21 illuminating exercise for those of us who  
22 participated, and highlighted just how much



1 some folks were relying on assumptions that  
2 certain animal tumor types were not relevant  
3 for humans based only on the perception that  
4 humans would not be exposed at sufficient  
5 levels to get these tumors rather than on the  
6 fact that there were true differences in  
7 physiology or biology.

8           The most important aspect of the  
9 framework for assessing the human relevance of  
10 animal cancer findings was that the failure to  
11 establish that an animal cancer mode-of-action  
12 could not occur in humans, resulted in the  
13 default assumption that the animal cancer  
14 finding was in fact relevant for human health  
15 assessment.

16           So, why is this fact important?  
17 In the current proposed framework for  
18 incorporation of data from in vitro/in vivo  
19 human incident in epidemiology data by its  
20 very nature, it creates to me the expectation  
21 that inconsistent findings in any one area  
22 could lead to inaction on the part of the

1 agency.

2           Consider, if you will, that  
3 uncertainty in any particular area, for  
4 example, the relevancy of a particular end  
5 point in an in vitro assay, say, in a high  
6 through-put screening assay, to the toxicity  
7 pathway that one thinks he or she is probing,  
8 for example, we know in fact as we go into the  
9 HTS programs, that we're trying to pick out  
10 targeted enzymes or targeted parts of toxicity  
11 pathways and probe those in ways that are  
12 meaningful. We're not sure, in fact, if those  
13 probes are hitting critical parts of those  
14 pathways or parts of those pathways that have  
15 a lot of play in them, for example.

16           Or if you look, for example, at  
17 human - or at animal cancer data, there are a  
18 number of end points that could show up as  
19 clearly positive, strong outcomes in animal  
20 cancer studies in, say, the Harderian gland or  
21 the Zymbal's gland or the forestomach, targets  
22 that do not have a clear human counterpart.

1                   So, one might consider that in  
2 fact these kinds of things are equivalent to  
3 the confounding in an epidemiology study. And  
4 I enter into that based again on the same fear  
5 that you had after talking - your earlier  
6 comments.

7                   But confounding as we all know in  
8 epidemiology studies, is often used to explain  
9 away findings, when in fact we know that it  
10 can also mean that the true signal is stronger  
11 than it appears because it's basically  
12 fighting through the fog.

13                  So, this is the main issue that I  
14 think EPA needs to be aware of and guard  
15 against when attempting to bring to bear all  
16 these different types of data in reaching  
17 public health decisions.

18                  By bringing all of the relevant  
19 data to the table, the EPA cannot raise the  
20 bar so high that nothing is recognized as a  
21 threat to public health.

22                  We heard yesterday assurances that

1 strong epidemiology signals wouldn't be  
2 ignored, but having more data and having more  
3 data of different types with different  
4 associations and strength of associations with  
5 the actual outcome that we're evaluating, can  
6 as easily lead to confusion as lead to  
7 clarity.

8           It's still going to come down, I  
9 think, to professional judgment of the  
10 strength of the data in the separate areas  
11 before a decision can be reached on the  
12 collective cohesiveness or biological  
13 plausibility of the data set that you're  
14 looking at predicting a human health outcome.

15           CHAIR HEERINGA: Thank you, Dr.  
16 Bucher.

17           Dr. Chambers.

18           DR. CHAMBERS: I don't have much to  
19 add and it certainly won't be as articulate as  
20 that was.

21           The opinions I had on this to add  
22 anything to it is that I think that in most

1 cases the epidemiology and the incident data  
2 will be mostly apical end points and will not  
3 look at the intermediate steps like the key  
4 events and the dose-response for the key  
5 events and the pathway. So, I think the  
6 information you'll be getting from the epi  
7 studies would be confirmatory for some of the  
8 animal research on mechanisms and action and  
9 so forth.

10 For the most part, I don't think  
11 you're going to get - I think the Bradford  
12 Hill are very good criteria, but I don't think  
13 you're going to get a lot of that information  
14 out of the epi studies that you don't get out  
15 of the animal studies.

16 CHAIR HEERINGA: Thank you, Dr.  
17 Chambers.

18 Dr. LeBlanc.

19 DR. LeBLANC: Most of my points  
20 have been covered. So, I'm going to try and  
21 avoid redundancy here, but I do want to echo  
22 Dr. Hayton's point that while I feel, as

1 everyone else dose, that the approach is very,  
2 very appropriate, I think that the various  
3 parameters within the Bradford Hill criteria  
4 have different weights and should be - these  
5 different weights should be applied when  
6 organizing the information and making  
7 judgements as to how the individual pieces of  
8 information should be used.

9           With reference to a couple of the  
10 criteria, one being consistency, it was noted  
11 in the framework that human and animal  
12 responses may not be consistent, and that  
13 certainly is the case.

14           And as I read it, the resolution  
15 to those situations would be to identify the  
16 most sensitive end point in the animal models,  
17 and to use that end point in decision making  
18 to assure protection of humans.

19           And I would suggest that perhaps  
20 as an alternative or in addition to that, one  
21 should simply look at the chain of events that  
22 occur that's pretty much identified in

1 establishing key events, and taking one step  
2 back on the rung.

3           So, for example, a chemical is  
4 inhibiting an enzyme. And in the rodent  
5 models, it's causing cardiac arrhythmia. And  
6 in humans, it's causing really nasty  
7 headaches, and you can't measure really nasty  
8 headaches in the rodent models.

9           Cardiac arrhythmia itself may not  
10 be appropriate, but you can take a step back  
11 and look at concentrations when that  
12 information is available, as to what level of  
13 enzyme inhibition causes the effects in the  
14 rodent models and what levels of enzyme  
15 inhibition occur in the human models, and make  
16 decisions that then sort of titrate with the  
17 results derived from the animal studies for  
18 the protection of humans.

19           I recognize that's difficult to do  
20 simply due to the lack of information most  
21 often in the epi studies.

22           Another point relates to the fact

1 that the epi studies may indicate other modes  
2 of action. You set up this paradigm, you have  
3 biological plausibility and everything works  
4 really well, and you have some well-designed  
5 epi studies that show effects, but they're not  
6 consistent. They question the - there's no  
7 biological plausibility to the effects that  
8 are observed.

9 And I think that's very important  
10 information. It may be of limited information  
11 from a risk assessment standpoint, but it  
12 certainly can't be ignored. I think what it's  
13 doing is just opening up new areas of  
14 investigation.

15 The epi studies perhaps could be  
16 categorized as - well, they could be  
17 categorized many ways, but there are certainly  
18 epi studies that are not good epi studies.  
19 And presumably, they would be triaged in the  
20 process early on.

21 There are other epi studies that  
22 are good studies. They're just not



1 predictable. They gave results that were  
2 unanticipated. A hypothesis was set, and the  
3 hypothesis wasn't supported, but good  
4 information is derived and I think that  
5 information is important.

6 It may suggest that based upon the  
7 Bradford Hill criteria, that certain box of  
8 confidence was developed and that this  
9 information falls beyond the box. It may  
10 indicate, then, perhaps that box needs to be  
11 widened.

12 So, from a regulatory standpoint I  
13 recognize that it is limited, but certainly  
14 can't be ignored. I think it has to provide  
15 guidance to new hypotheses, to new studies, to  
16 new analyses of existing studies. That's all  
17 I have.

18 CHAIR HEERINGA: Dr. Bailar.

19 DR. BAILAR: I don't have much to  
20 add. One thing is to emphasize something I  
21 mentioned yesterday, is the original purpose  
22 of these criteria was to bring some order and

1 rationality and interpretability to a very  
2 difficult art, and it is an art, of trying to  
3 interpret observational data.

4 Now, Dr. Weed has pointed out that  
5 even that Surgeon General's report was not the  
6 first in the field. He has written about it  
7 in his textbook, the prior history, but it is  
8 a very difficult kind of thing to do.

9 Hill himself did not stick  
10 rigorously to this criteria. He modified them  
11 in response to specific issues that came up in  
12 things he was looking at. They have to be  
13 interpreted flexibly. And as Dr. Hayton said,  
14 it should not be taken as a checklist.

15 I really emphasize the need for  
16 flexibility in applying these. Add things,  
17 subtract things, modify them further as needed  
18 to suit a particular problem.

19 Another point is that on Page 28  
20 you refer to the literature search, but you do  
21 not say how that search will be organized and  
22 conducted. And it does not refer to the

1 necessary screening of papers to find those  
2 that have some merit for whatever your present  
3 purpose is.

4 I've written somewhere else about  
5 the characteristics of data that I've noticed  
6 in big, public problems. One is that the data  
7 tends to be vast. Just enormous amounts of  
8 stuff available.

9 The second is that they tend to be  
10 highly complex in that there are all kinds of  
11 issues. They often involve many, many  
12 different kinds of scientific and technical  
13 expertise. You have to have a way to deal  
14 with that complexity.

15 The third is that almost  
16 everything you'll find is of poor quality. It  
17 has to be screened out or at least weighed so  
18 that it's severely down weighted.

19 And the fourth is that it's often  
20 not what you want anyway.

21 In the literature search, I think  
22 you might want to deal with this and bring out

1 points, not necessarily exactly these, but how  
2 the literature search should be conducted and  
3 how the results should be interpreted and  
4 dealt with.

5 The third point is that you refer  
6 to the postulated mechanism of action, but you  
7 don't really deal with the difficulties of  
8 determining the mechanism of action with  
9 reasonable certainty, or how the residual  
10 uncertainty should be dealt with in the  
11 analysis.

12 A further problem is that there  
13 may be special difficulties when there are two  
14 or more outcomes of concern that seem to have  
15 different mechanisms of action and how you're  
16 going to deal with them. Thank you.

17 CHAIR HEERINGA: We turn now to  
18 other members of the panel for any comments.

19 Yes, Dr. Greenwood, please.

20 DR. GREENWOOD: I think the use of  
21 the Bradford Hill, as he called them, I think,  
22 review points rather than criteria, it is a

1 very sound way of approaching what is a very  
2 complicated set of systems.

3 But one of the things that hit me  
4 yesterday listening to the input that we  
5 received, was that if you were to look at  
6 plausibility before you looked objectively at  
7 the outcomes of your assessment of studies  
8 which you are looking at, that it could  
9 actually change your objectivity.

10 And that is a danger, I think.  
11 And it was brought home to me by the way that  
12 people were looking at the atrazine data and  
13 the responses in that.

14 I think that it's very important  
15 to look at the plausibility, the biological  
16 plausibility, but I think that probably needs  
17 to be looked at after an objective assessment  
18 of the value of the study rather than before.

19 Because none of us wants to do  
20 work that we don't really have to do, and it's  
21 very easy, actually, to throw something out if  
22 you've got a good reason for not looking at it

1 too carefully because it didn't seem  
2 plausible. And I think you might miss  
3 important factors if you were to look at the  
4 plausibility and let that influence your  
5 assessment of the data that you're looking at.

6 CHAIR HEERINGA: Thank you, Dr.  
7 Greenwood.

8 Dr. Reed.

9 DR. REED: I want to say thank you,  
10 Dr. Greenwood, for bringing this up. I think  
11 this is the area that we are most afraid of.  
12 It's predetermining what is biologically  
13 plausible, what is not.

14 And then in the next step we have  
15 the other mode-of-action, and so the two might  
16 come working against each other. You already  
17 write it off on the plausibility, and then you  
18 have a new mode-of-action of possibly the new  
19 manifestation of the same mode-of-action that  
20 may be different between animals and humans,  
21 and you write that off too.

22 So, I really appreciate that

1 comment. I think it's important to be  
2 objective about plausibility.

3 CHAIR HEERINGA: Dr. Reif.

4 DR. REIF: Just not a disagreement,  
5 but a note of caution because in epidemiology,  
6 I think most of us try to do hypothesis-based  
7 research. And part of our - the formation of  
8 epidemiologic hypotheses does in fact rest on  
9 biological plausibility.

10 So, we find ourselves in a bit of  
11 a conundrum if we say to ourselves well, I'm  
12 just going to go and do an exploratory data  
13 dredging without having the recognition of at  
14 least some awareness of what happens in animal  
15 systems.

16 So, I just throw that out as a  
17 note of caution on the biological plausibility  
18 issue.

19 CHAIR HEERINGA: Dr. Reif, on that  
20 topic, and also Dr. Reed, Dr. Reed mentioned  
21 there is the sequence. There is the  
22 biological plausibility criterion or element.

1 And then follow that, I assume if you reject,  
2 then you move on to is there another mode-of-  
3 action which would explain, and cycle back.

4 Is that -

5 DR. REED: Mostly I think it's  
6 important to have a placeholder for something  
7 that you're looking, that you're puzzling  
8 about. It's more of a benefit of doubt kind  
9 of way of looking at data and I think it's  
10 important.

11 CHAIR HEERINGA: Is that  
12 appropriately placed at the end? In other  
13 words - Dr. Bove, you look like you -

14 DR. BOVE: I was just going to say  
15 that another word of caution is that the  
16 biological plausibility evolves over time and  
17 changes so that what we think is not  
18 biologically plausible today, becomes  
19 biologically plausible.

20 So, it's true we develop our  
21 hypotheses that way, but we also leave it open  
22 sometimes to evaluate the data. It's not



1 really a dredging exercise. We still have a  
2 hypothesis. We just don't have biological  
3 plausibility for it.

4 For example, in the early days we  
5 were looking at disinfection byproducts. None  
6 of us thought that there was an association  
7 with birth defects or with small for  
8 gestational age. There was no biological  
9 plausibility at the time. And the research  
10 developed because of findings that way.

11 These were hypothesis driven, but  
12 there wasn't much biological plausibility.  
13 Since then, you know, research has developed  
14 since then.

15 CHAIR HEERINGA: Dr. Lu.

16 DR. LU: I just want to comment. I  
17 might be the least qualified person to comment  
18 on this, but I do believe that we have to lose  
19 this co-called modified Bradford Hill  
20 criteria. Because in my opinion, the  
21 principle of epidemiology was developed to  
22 study incidents like infectious disease, like

1 which wells that contain cholera, the bacteria  
2 that cause cholera and so on and so forth.

3 When we deal with these issues  
4 that involving chemical exposures, especially  
5 the chemical that come and goes and to create  
6 an environment, I mean nothing really fit into  
7 the criteria.

8 So, if the agency is bounded to  
9 these modified criteria that, you know, it can  
10 really go out of the box and seek for other  
11 evidence.

12 And as Dr. Bove just suggested,  
13 and we actually talked about it yesterday,  
14 that the biological plausibility evolved.

15 I still remember we talk about  
16 melamine case. If you ignore the incident  
17 data, then melamine would still be able to  
18 added to the plot, but it's the incident data  
19 that actually raised the red flag and then  
20 lead to a lot of regulatory action.

21 So, I mean in this case it doesn't  
22 fit into the Bradford Hill criteria, and you

1 will pretty much ignore the incidents of the  
2 melamine data.

3               So, I mean I'm going to talk about  
4 a little bit more about this when we get to  
5 Question 2, but my position here is that it's  
6 a criteria that for the reference. But if you  
7 can bind yourself into this, I don't think  
8 it's a wise move.

9               CHAIR HEERINGA: Dr. Meek.

10              DR. MEEK: Could someone define  
11 "biological plausibility" for me? I think  
12 there's a real issue in terms of how people  
13 are interpreting biological plausibility  
14 around the table and I think we're talking at  
15 cross-purposes.

16              DR. LU: Right. I mean my  
17 definition is a disease caused by certain  
18 chemical exposures.

19              DR. MEEK: I think it's the issue  
20 that Dr. Gold raised yesterday, and I think we  
21 used biological plausibility in an  
22 epidemiological context completely differently

1     than we would use it in either a toxicological  
2     or a mode-of-action context.

3                     And the criteria with which I'm  
4     most familiar in terms of the Bradford Hill  
5     criteria being applied in a mode-of-action  
6     context, really means do the data support.  
7     And in the more generic biological data, do  
8     they make, you know, does what you're seeing  
9     make sense?

10                    So, I think we're really talking  
11    at cross-purposes in terms of biological  
12    plausibility.

13                    I'm not entirely sure how  
14    biological plausibility could ever be used as  
15    a barrier for not considering any fact, so I  
16    didn't really understand much of that  
17    discussion.

18                    CHAIR HEERINGA: Well, how do we  
19    sort this out?

20                    Dr. Gold.

21                    DR. GOLD: Well, I wanted to make a  
22    comment about that, and also about using the

1 criteria, but they relate to each other.

2 I agree with the comments that  
3 were made that you don't weight all the  
4 criteria necessarily equally. And in terms of  
5 biologic plausibility, I think when these  
6 criteria were developed and published and so  
7 forth, a lot of it was around the smoking and  
8 cancer relationship.

9 And we didn't have the  
10 pathophysiologic mechanisms by which smoking  
11 caused lung cancer, but that didn't prohibit  
12 action in terms of public health education and  
13 smoking cessation efforts and so forth.

14 And by the way, you could still  
15 maybe even do trials to see, you know,  
16 preventive trials. That might shore up your  
17 causal argument. So, I think we need to be  
18 careful about how we weight them.

19 One other comment, and then I'm  
20 going to come back to the biologic - so, I  
21 think even some of these criteria have fallen  
22 out of favor, for example, the specificity of

1 the association of the exposure-disease  
2 association, because a lot of exposures that  
3 we're talking about have systemic effects.

4 And so we don't see specificity of  
5 the association, and I think that one in  
6 particular has - I'm not saying that it  
7 shouldn't be in the list, but has brought -  
8 should get considerably less weight in most  
9 circumstances.

10 And then with regard to the  
11 biologic plausibility, I just think that when  
12 the toxicologists talk about it, I think  
13 they're talking about it differently than  
14 perhaps when the epidemiologists or the  
15 biologists are talking about it.

16 And maybe there needs to be  
17 recognition in the document that different  
18 disciplines are speaking here and they come at  
19 this with different viewpoints and  
20 interpretations, and maybe there needs to be  
21 some clarification from those different  
22 viewpoints.

1                   But I also think that lack of -  
2   apparent lack of biologic plausibility does  
3   not necessarily mean that you don't have  
4   enough evidence to take action.

5                   CHAIR HEERINGA: We'll go to Dr.  
6   Lowit, and then Dr. Bove.

7                   DR. LOWIT: I was glad to see Dr.  
8   Meek speak up, because I was having trouble  
9   following the line of some of the discussion.  
10   And I'm quite uncomfortable with the idea that  
11   biological plausibility is a yes or no answer  
12   that really thrives in the face of the idea of  
13   evaluating the totality of the information  
14   across multiple lines of evidence and to  
15   understand the strengths and the weaknesses.

16                  And sometimes those weaknesses can  
17   tell you as much as the strengths do in that  
18   there's - at least as we see it, that there is  
19   nothing about the use of the framework as  
20   written that precludes action when you have a  
21   robust data set for which you have maybe a  
22   mismatch across the humans and animals that

1     you take a public health eye and you take  
2     action in that appropriate way.

3                     And that's actually the power of -  
4     the transparency of the framework is that you  
5     can lay that evidence out and talk about your  
6     uncertainties and your strengths and how you  
7     came to a particular conclusion.

8                     So, I hope we continue this  
9     discussion about the plausibility issue.

10                    CHAIR HEERINGA: Dr. Bove, and then  
11     Dr. Bailar.

12                    DR. BOVE: Yes, remember they're  
13     viewpoints. And as viewpoints for having a  
14     discussion about causality, they're important  
15     to take into consideration, but Hill never  
16     thought of them as something that you rule  
17     out.

18                    I think the only thing that rules  
19     out is temporality. That's the only one. The  
20     other ones don't rule out anything. They're  
21     just issues that should be raised. Some of  
22     them, anyway, and some shouldn't be raised



1 because they're not relevant.

2 And when you say it makes sense,  
3 there's enough uncertainty throughout  
4 toxicology and it's hard for me to say well,  
5 what makes sense. And, again, that evolves as  
6 well.

7 So, I don't think we're talking at  
8 cross-purposes. I think what we're saying is  
9 that, you know, just what you said. It's not  
10 a yes, no, that biological plausibility is  
11 something to think about, but that we also are  
12 aware there's plenty of uncertainty about  
13 biological plausibility and that the knowledge  
14 evolves.

15 CHAIR HEERINGA: Dr. Bailar.

16 DR. BAILAR: I think the biologic  
17 plausibility in terms of health - how do you  
18 evaluate the likelihood that this is going to  
19 be a real effect?

20 In terms of the, you know, the  
21 statisticians would deal with what's the prior  
22 probability based on what you already know?

1           Things like possible mechanisms of  
2   actions, what you know about related  
3   compounds, what you know about potential  
4   confounders, try to integrate all that to get  
5   at least a general sense of is this a place  
6   where you would be surprised by finding an  
7   effect or is it a place where you really might  
8   sort of expect an effect?

9           I don't know that you could really  
10   be any more precise than that in terms of  
11   plausibility.

12           CHAIR HEERINGA: Dr. Reed.

13           DR. REED: I think this discussion  
14   is very helpful. I think when we look back at  
15   the document, maybe we can - because some of  
16   it captures some of this discussion a little  
17   bit on Page 31 on the bullet about biological  
18   plausibility, because it was more specific to  
19   a known mode-of-action.

20           And so that might be part of the  
21   confusion. So, that would be what I would  
22   recommend.

1                   CHAIR HEERINGA: I'd like to move  
2   on to Question 1.4, there is a relationship  
3   here, before the noon hour. I don't want to  
4   lose track of this line of discussion.

5                   And so if there are additional  
6   thoughts on the part of the panel members on  
7   not only the criterion, but the sequencing and  
8   the action steps.

9                   One thing that I heard, and I'm  
10   somewhat of a naive listener here, is that  
11   there's some emphasis on differential  
12   weighting of these criteria. There's some  
13   emphasis on qualitative interpretation.

14                  I know from having sat here, that  
15   there will never be enough data to decisively  
16   address any one of these criteria in most of  
17   these investigations. So, there's a missing  
18   data problem.

19                  And I think that one thing we  
20   ought to think about is that this is a  
21   framework. So, is it organizing or is there  
22   more of a decision rule theoretic-type

1 approach? I suspect that answer will be  
2 rejected.

3 So, where do we draw the line  
4 stepping back where this essentially sort of  
5 devolves into yes, we followed these steps,  
6 they proved inadequate, so we're going to fall  
7 back on sort of an arbitrary decision.

8 It's just a thought that I had  
9 listening to the process here. So, I think we  
10 need to be at least in terms of each of these  
11 steps and the criteria and the potential  
12 weighting and interpretation, as clear as we  
13 can be in our reporting.

14 So, let's turn to Question Number  
15 1.4.

16 MR. DAWSON: Question 1.4, OPP has  
17 extensive experience applying the mode-of-  
18 action framework to experimental animal data.  
19 However, OPP has not yet completed a WOE  
20 approach that also includes epidemiology or  
21 human incident data like that proposed in  
22 Section IV of the draft framework. Please

1 include in your comments what, if any,  
2 additional scientific considerations not  
3 discussed in the draft framework OPP should  
4 take into account when conducting such WOE  
5 analyses.

6 CHAIR HEERINGA: Dr. Meek.

7 DR. MEEK: Thank you. I think  
8 we've probably largely addressed the content  
9 of 1.4 in the previous discussion, but one  
10 other thought comes to mind when I was  
11 listening to the discussion on biological  
12 plausibility.

13 One of the aspects that seems  
14 relatively important here is to be  
15 characterizing relative degrees of uncertainty  
16 in the various components of the database and  
17 how we relate them one to another in an  
18 overall framework analysis.

19 We can really only characterize  
20 that uncertainty relative to other data sets  
21 that we know, and there are no absolutes. So,  
22 there are no yes/no answers.

1                   So, I think it's probably really  
2   important to do that to the extent that we can  
3   in doing these framework analyses. So, what's  
4   the extent of the data in each of the areas  
5   and what's our overall confidence in our  
6   conclusions?

7                   CHAIR HEERINGA: Thank you, Dr.  
8   Meek. That's a better way of saying what I  
9   was trying to say before.

10                  Dr. Bucher.

11                  DR. BUCHER: No, I agree and I  
12   don't really have anything to add to what  
13   Bette said.

14                  I think the important thing is to  
15   try to get across maybe in the document, a  
16   little better idea of how one would handle  
17   situations where different types of data that  
18   either agreed or disagreed would be handled,  
19   how you would try to weight different types of  
20   information against one another.

21                  That's very difficult to do  
22   without some examples of exactly what one

1 might do in different cases.

2 CHAIR HEERINGA: Dr. Reif.

3 DR. REIF: Well, the question asks  
4 for additional scientific considerations not  
5 considered, and let me just address the issue  
6 of individual susceptibility first from an  
7 epidemiologic perspective.

8 Of course this notion has been  
9 around for a long, long time if one goes back  
10 to the smoking question. Critics of the  
11 association between cigarette smoking and lung  
12 cancer pointed to people who smoked two packs  
13 a day for 50 years and died of a broken heart,  
14 as I sometimes describe it to students.

15 But in a more modern context, the  
16 issue of susceptibility and genetic variation,  
17 I think, is an important one that hasn't been  
18 addressed in the document. And no doubt as  
19 you heard yesterday, is being incorporated  
20 into good epidemiologic studies like the  
21 agricultural health study.

22 So, the addition of some

1 discussion of genetic variability in terms of  
2 SNPs or in terms of genome-wide association  
3 studies from a human side and the  
4 incorporation of knockouts.

5 And I'm not aware of the extent to  
6 which those sorts of studies are done today,  
7 for example, at NTP, but I do believe that we  
8 would be remiss if we didn't anticipate within  
9 a very short period of time, or actually  
10 currently the appearance of studies, both  
11 human and animal, that incorporate genetic  
12 analyses using the contemporary techniques.

13 So, that's my suggestion for  
14 additional scientific considerations that  
15 might be helpful.

16 CHAIR HEERINGA: Dr. Hayton.

17 DR. HAYTON: the only thing I  
18 thought might be missing from Section 3 was an  
19 explicit statement of intention to estimate or  
20 quantify exposure or the dose.

21 CHAIR HEERINGA: Comments from  
22 other panel members? And feel free to return



1 to the previous topic, too.

2 Dr. Portier.

3 DR. PORTIER: I just wanted to  
4 reiterate what Dr. Reif said. I was sitting  
5 here thinking that the American Cancer Society  
6 has done cohort studies for over 40 years now,  
7 and we have a new one in place. And the new  
8 cohort concentrates highly on collecting blood  
9 samples for exactly the reasons he's talking  
10 about.

11 Even though it's a prospective  
12 study, you can't do a modern, expensive, long-  
13 term epidemiology study without collecting  
14 biospecimens for genetic analysis. So, that  
15 data is coming down the line.

16 CHAIR HEERINGA: Comments on these  
17 issues? Question 1.4, anything missing  
18 scientifically from the discussion of the  
19 frameworks?

20 Turn to Dr. Lowit, Jeff Dawson,  
21 Dr. Manibusan on this. Any points of  
22 clarification, something that confused you on?

1 DR. LOWIT: Not to re-open, but as  
2 you work through your report, this issue, the  
3 biological plausibility issue, I think Dr.  
4 Meek's point was right on that people coming  
5 from different discipline areas think we're  
6 thinking about that concept in a very  
7 different way.

8 And to the extent that there's  
9 discussion around those issues, would be  
10 helpful.

11 CHAIR HEERINGA: Dr. Bailar.

12 DR. BAILAR: That comment is right  
13 on target. I talked earlier about prior  
14 probability in relation to biologic  
15 plausibility. Different people will have  
16 different priors. That's just a fact of life.

17 CHAIR HEERINGA: Dr. Portier.

18 DR. PORTIER: Something that came  
19 to mind in researching the Bradford Hill  
20 criteria, and there's one other thing that  
21 kind of came up that we haven't really talked  
22 about, which is the concept of analogy, using

1 in the risk assessment, information on similar  
2 chemicals, not specifically the one being  
3 studied, but ones where we've already studied  
4 and have a lot of information in kind of  
5 bringing that information into the decision-  
6 making process.

7 And in the whole weight of  
8 evidence approach, I didn't see any discussion  
9 on using chemical analogies, bringing in  
10 analogous chemicals into the discussion  
11 process.

12 So, I think you might want to add  
13 that as well.

14 CHAIR HEERINGA: Dr. Hayton.

15 DR. HAYTON: That makes me think it  
16 could also be pathway disruption. I mean it  
17 wouldn't have to be chemically similar, but  
18 what if it were - you could also look at your  
19 categorize on the basis of pathway effects  
20 rather than chemical class. Just another way.

21 CHAIR HEERINGA: You mean like  
22 endocrine systems or things like that?

1 DR. HAYTON: Yes, like endocrine  
2 disruptors which might not be chemically  
3 similar, but act on a common pathway.

4 CHAIR HEERINGA: I think that we  
5 have returned almost to the agenda schedule.  
6 Not that that's that important, but I think  
7 everybody deserves a long lunch. And so let's  
8 plan to reconvene at 1:00 p.m.

9 Thank you, everyone.

10 (Whereupon, the above-entitled  
11 matter went off the record at 11:38 a.m. and  
12 resumed at 1:00 p.m.)  
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A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:00 p.m.

CHAIR HEERINGA: Good afternoon,  
everyone. Welcome back to our afternoon  
session, second day of the FIFRA Science  
Advisory Panel meeting on the topic of the  
draft framework and case studies on atrazine,  
human incidents and the agricultural health  
study.

We are in the process of the  
response by the panel to the charge questions.  
And we have through this morning's session,  
covered Charge Questions 1 and its four parts.  
And we're ready now, I think, to turn to  
Charge Question 2A, which relates to the first  
of the case studies.

So, either Jeff or Dr. Lowit.

DR. LOWIT: Let's see. As  
discussed in Question 1.1, the draft framework  
provides general descriptions of the strengths  
and limitations of ecologic and retrospective  
epidemiology studies with respect to human

1 health risk assessment. Please describe what  
2 you consider to be characteristics of robust,  
3 well-designed ecologic and retrospective  
4 epidemiology studies.

5 CHAIR HEERINGA: And Dr. Gold is  
6 our lead discussant.

7 DR. GOLD: I'm afraid I have quite  
8 a bit to say. Some of it we touched on this  
9 morning, so I apologize in advance that it's  
10 long.

11 And the other thing is that in  
12 addition to answering what we need for robust  
13 and well-designed studies, I'm also going to  
14 say something about what I think is a little  
15 bit missing in the parts here. So, that's  
16 part of the reason for the length.

17 So, the first thing which won't  
18 directly answer that question is that I think  
19 we need clarity in the terms that we're using.  
20 So, the term "retrospective epidemiology  
21 studies," I think we need greater  
22 clarification because many epidemiology

1 investigators use this term to describe case  
2 control studies, as was mentioned this  
3 morning, because the information about  
4 exposure is gained retrospectively in these  
5 types of studies.

6               However, the term "retrospective"  
7 is also used in the framework for  
8 retrospective cohort studies, which is a  
9 different design, but could be considered  
10 retrospective because the exposure cohorts are  
11 assessed retrospectively.

12              So, case control studies and  
13 retrospective cohort studies can share some of  
14 the same challenges of accuracy and  
15 completeness of retrospectively ascertained  
16 exposure information, but they sometimes  
17 determine exposures differently or use  
18 different methods.

19              For example, in case control  
20 studies, frequently participants are asked  
21 about their prior exposures, which may suffer  
22 from inaccuracy in recall. In retrospective

1 cohort studies, the exposed and unexposed  
2 cohorts can, not always, but are often  
3 identified by existing records about prior  
4 exposure.

5           For example, in occupational  
6 studies, this is frequently the case. And so  
7 records may have the potential to be more  
8 accurate, not necessarily, and complete than  
9 participant recall of exposures.

10           Also, it should be noted that  
11 nested case control or case cohort designs  
12 would provide less potential for bias in  
13 ascertainment of exposures than would case  
14 control or retrospective cohort studies that  
15 depend on recall of exposures.

16           And just a really minor point that  
17 I quibble with the use of the term  
18 "predictors" in this section, because in  
19 ecologic or cross-sectional studies it's not  
20 always clear that we're talking about things  
21 that preceded - exposures that preceded  
22 disease occurrence. So, it's not necessarily



1 a predictor.

2 So, and then in the portion where  
3 ecologic studies are summarized on Page 41,  
4 much of the data on occurrence of birth  
5 defects, pre-term delivery and small for  
6 gestational age are derived from birth defects  
7 registries, birth records and national data  
8 sets.

9 So, important considerations in  
10 ecologic studies using such data sources, I  
11 have several of these, include; number one,  
12 whether reporting to the registry or on the  
13 birth record is mandatory as would - this  
14 would tend to make these sources of  
15 information more complete, and reporting from  
16 areas where it is not mandatory could be  
17 influenced by factors that might also be  
18 related to exposure, for example,  
19 socioeconomic status or may be related both to  
20 likelihood of reporting and exposure to  
21 pesticide.

22 Second, whether the registry is

1 actively identifying birth defects where it  
2 depends on passive reporting will affect how  
3 complete the ascertainment of cases is.

4 Third, reporting to the database  
5 depends on who reports. Because the more the  
6 reporting from different sources, the greater  
7 likelihood of more complete ascertainment.

8 Fourth, whether the criteria in  
9 definitions of birth defects, pre-term  
10 delivery and small for gestational age has  
11 been explicit and consistently used so they're  
12 comparable across years and regions.

13 And finally, what was the length  
14 of follow-up for birth defects? For example,  
15 was it just at birth or for one year? This  
16 will greatly affect how complete the  
17 ascertainment is.

18 So, to answer the question,  
19 robust, well-designed ecologic or  
20 retrospective studies should derive  
21 reproductive outcome data either from  
22 registries with mandatory reporting and active

1 surveillance with explicit and consistently  
2 used criteria and definitions of outcomes for  
3 ecologic studies or routine regular screening  
4 for outcomes in exposed and unexposed cohorts  
5 with explicit and consistently used criteria  
6 and definitions of those outcomes in these  
7 retrospective studies.

8 I have some additional  
9 considerations for information on confounding  
10 variables, whether they were obtained and  
11 controlled in statistical analyses.

12 So, this is important when you're  
13 comparing rates across geographic areas or  
14 between a state and the United States as a  
15 whole, because differences in the population  
16 distributions with regard to such factors, and  
17 I have a whole list of them, could affect the  
18 rates. They may be small, but need to be  
19 examined. And, thus, influence the  
20 determination of the difference in rates  
21 between the areas being considered.

22 In the case of ecologic studies,

1 this is further influenced by the fact that  
2 adjustment for confounding at the population  
3 level may not sufficiently remove confounding  
4 effects, and, thus, result in differences from  
5 studies in which confounding factors are  
6 adjusted on an individual basis to obtain  
7 summary statistical results for comparing  
8 groups.

9           Also, in some of the examples that  
10 were cited, the CDC natality database was used  
11 and they do adjust for confounding factors,  
12 but some of these factors are missing in  
13 certain states.

14           And so they're not comparable over  
15 years or they may not be comparable - the  
16 results when you adjust for the confounders  
17 may not be comparable across different states.

18           So robust, well-designed ecologic  
19 or retrospective studies should obtain  
20 complete information on as many potentially  
21 confounding variables as possible from all  
22 groups in the case of ecologic studies, or all

1 individuals in the case of retrospective  
2 studies, and evaluate them as to their  
3 relation to exposures and outcomes and their  
4 modification of the exposure/outcome  
5 relationships. So, it's not just confounding,  
6 but effect modification as well.

7           Also mentioned in this section,  
8 referring to Page 41 of the framework,  
9 generally involved surrogate measures of  
10 exposure, for example, levels in the drinking  
11 water, proximity to fields and so forth,  
12 rather than measures of actual exposures.  
13 Don't measure how much women actually drink or  
14 measures at the tap, for example.

15           So robust, well-designed ecologic  
16 or retrospective studies should use the best,  
17 possible measures of exposure that are most  
18 likely to relate directly to the outcome, for  
19 example, drinking water measures instead of  
20 ground or surface water measures, as  
21 individual amounts of tap water and bottled  
22 water consumed as well.

1                   Another issue related to the use  
2 of surrogate measures of exposures is that  
3 studies of reproductive outcomes often use the  
4 place of residence of the mother at time of  
5 birth to relate to environmental exposures by  
6 area, and studies of chronic diseases often  
7 use the address at the time of diagnosis.

8                   So, use of these addresses, I  
9 don't think we did discuss this earlier today.  
10 The use of these addresses can result in  
11 misclassification of the relevant area of  
12 residence. For example, in the reproductive  
13 studies, residence at conception depending on  
14 which outcome you're looking at, might be more  
15 relevant than where the mother is living at  
16 the time of birth.

17                  And so in robust, well-designed  
18 ecologic or retrospective studies, we should  
19 acquire residential histories whenever  
20 possible. That's very difficult to do, I  
21 realize. More likely to be done in  
22 retrospective studies than ecologic studies,

1 and even in retrospective studies it's  
2 difficult.

3           So, the purpose would be to use  
4 the most relevant residential location for  
5 assessing exposure, although it would be noted  
6 that even obtaining relevant residential  
7 location may misclassify individual exposures  
8 because individuals spend substantial portions  
9 of their lives at work or otherwise away from  
10 their residences and the exposures in these  
11 locations are often not considered.

12           I think this was mentioned  
13 yesterday, but not today: Care should also be  
14 taken to consider different health outcomes  
15 separately. For example, different kinds of  
16 birth defects may have different etiology or  
17 a different relationship to the agent under  
18 study. And the birth defects will have  
19 different relationships, potentially, than  
20 birth weight, pre-term delivery or small for  
21 gestational age, because the etiologic  
22 mechanisms may differ.

1                   So robust, well-designed ecologic  
2 or retrospective studies should provide  
3 sufficient sample size to have adequate  
4 statistical power to examine the relation of  
5 exposure to different outcomes separately as  
6 they may have different etiologic mechanisms.

7                   Let's see. Some additional  
8 considerations in ecologic studies, and this  
9 is highlighted, actually, in Table A2 on Page  
10 43, that there are some quite large sample  
11 sizes there.

12                   So, sometimes when you're  
13 comparing populations, you can end up with  
14 huge populations. I think there were over 30  
15 million births in one of the studies.

16                   So, this can result in very small  
17 differences being statistically significant.  
18 And what needs to be decided is if they're  
19 really meaningful or clinically or public  
20 health-wise important.

21                   So in robust, well-designed  
22 ecologic or retrospective studies, it would be



1 important to consider whether the magnitudes  
2 of the differences are truly meaningful, and  
3 whether the differences could be due to  
4 uncontrolled confounding and whether the  
5 differences are internally consistent.

6 I have a couple more - no, one  
7 more. So, another important consideration for  
8 ecologic studies, and sometimes for  
9 prospective and retrospective cohort studies,  
10 is that if multiple outcomes are examined, for  
11 example, different types of birth defects or  
12 multiple associations, for example, using  
13 different timing and measures of exposure, if  
14 you're testing those multiple outcomes,  
15 multiple associations in relation to an  
16 exposure, then some associations are going to  
17 be statistically significant by chance alone  
18 due to multiple testing.

19 So, in such circumstances for the  
20 ecologic or retrospective studies to be  
21 considered robust and well-designed,  
22 investigators should account or adjust for

1 multiple testing unless a strong hypothesis  
2 indicates the likelihood of the exposure being  
3 related to more than one outcome.

4 That's all I have.

5 CHAIR HEERINGA: Thank you, Dr.  
6 Gold.

7 Dr. Bove.

8 DR. BOVE: I have a few things.  
9 The first thing is that if you do a birth  
10 defect study in this day and age, you should  
11 use a population-based birth defect registry.  
12 And if you're going to look at the birth  
13 certificates, look at your state's birth  
14 certificates. I mean I don't understand why  
15 you need to go elsewhere or national databases  
16 when these are available, certainly, the  
17 health departments, and that might help with  
18 the ascertainment issue.

19 There are a couple of other  
20 issues. Again, a lot of criticisms at these  
21 studies are that there was confounding bias or  
22 selection bias or exposure, misclassification

1 bias, and sometimes they're there, and  
2 sometimes they're not. But it would be  
3 helpful if a case is made as to whether they  
4 exist, and some effort made to determine what  
5 the impact might be of unmeasured confounders,  
6 for example.

7 As I said earlier today, a  
8 significant confounding is a rare event,  
9 actually. And it would be good to get a  
10 handle on just what impact confounders will  
11 have and whether it would really change the  
12 interpretation of the data.

13 Speaking of interpretation of the  
14 data, I mentioned earlier, too, that the  
15 reliance on statistical significance to  
16 determine whether a finding is worth looking  
17 at or not is a bad approach. And that also  
18 part of the problem with multiple comparisons  
19 is just that, that you're busy looking at  
20 statistically significant findings, and even  
21 worse you penalize findings because you worry  
22 about multiple comparisons, and really that's

1 not what you should be evaluating.

2           You miss quite a number of good,  
3 important findings if you're focused only on  
4 statistical significance. Studies often are  
5 under-powered for birth defects.

6           So, if you're going to focus on  
7 statistical significance and determine whether  
8 you're going to take something seriously or  
9 not, then you know the answer before you do  
10 the study. If we don't have enough power,  
11 none of these things will be statistically  
12 significant, so why bother even doing the  
13 study in the first place.

14           The reason you do a study in the  
15 first place is because that's not what you're  
16 supposed to focus on. You're supposed to  
17 focus on the magnitude of the association.  
18 That's the odds ration, the relevant risk,  
19 point estimate, the coefficient regression and  
20 so on so forth.

21           Certainly a confidence interval is  
22 important, but if you look at just one end of

1 the confidence interval, you're wasting your  
2 time. You might as well not calculate it at  
3 all.

4 There are two ends to a confidence  
5 interval, and I think that there are other  
6 issues that make you want to look at a finding  
7 and take it seriously or not, and statistical  
8 significance shouldn't be one of them.

9 Okay. And I think that part of  
10 the problem with some of the evaluations of  
11 these studies by the EPA and by the  
12 researchers themselves, fall into this trap of  
13 using statistical significance as a yes/no,  
14 whether I'm going to take it seriously and  
15 failure to look at exposure-response  
16 relationships that aren't statistically  
17 significant, but actually indicate that there  
18 may be something there. Enough on that.

19 So, some of the studies actually  
20 didn't report findings because they weren't  
21 statistically significant. That's unfortunate  
22 as well.

1 I do think that drinking water  
2 studies are difficult to do, but I do think  
3 that if it's possible to use the monitoring  
4 data and do some sophisticated modeling, we  
5 can actually get down to monthly estimates of  
6 contamination, which fit well in evaluating  
7 trimester or exposure.

8 Granted, we don't have information  
9 oftentimes on bottled water use. But if the  
10 contaminants are volatile, there's a showering  
11 exposure and dermal exposure at least as  
12 important as well.

13 So, I do think drinking water  
14 studies are extremely valuable, and so are air  
15 pollution studies as well, if you can use the  
16 monitoring data and use sophisticated modeling  
17 to estimate what those exposures are. And I  
18 think for past exposures, that's pretty much  
19 what you have to do in order to estimate  
20 exposures.

21 I do take exposure-response  
22 relationships very seriously. I think that

1 researchers should too. I think that they  
2 should look at smoothing methods to see if the  
3 categorization made sense. I don't think they  
4 should just throw a continuous variable into  
5 a regression model, especially an exponential  
6 model. I think they need to see if the way  
7 they've categorized it or the way they're  
8 portraying exposure-response relationship  
9 actually is nearing the actual curve itself.

10 At the end of the day, I think  
11 it's important for the study to have a study  
12 design that matches what the objectives of the  
13 research are.

14 If a study really wants to look at  
15 effect modification, then it needs to be  
16 appropriately designed so it can look at  
17 effect modification, because that is a  
18 hypothesis and just as important maybe as the  
19 usual hypothesis we look at when we look at  
20 exposure-deceased relationships. So, that's  
21 about it.

22 CHAIR HEERINGA: Thank you, Dr.

1 Bove.

2 Dr. Reif.

3 DR. REIF: I think my colleagues  
4 have done a very thorough job in answering the  
5 specific question here under 2.1. And what  
6 I'd like to do for just a second, is to step  
7 back and just add a little bit to the general  
8 framework of reproductive epidemiology  
9 especially in the first - in the early stages  
10 of exploring exposure-outcome relationships.

11 So, going back to what we  
12 discussed this morning however you'd like to  
13 define "biological plausibility," supposing  
14 that there's evidence from animal studies that  
15 there are reproductive effects in laboratory  
16 animals, but that the likelihood is that the  
17 epidemiologic database for a specific chemical  
18 or pesticide is going to be sparse.

19 So, if one begins to think about  
20 the potential effects in humans to evaluate  
21 concordance, then one should take a broad  
22 approach to the various end points that



1 reproductive epidemiologists use.

2           So, for example, going to some  
3 things we haven't talked about, assessment of  
4 fertility in any of these designs, not in  
5 ecologic, but certainly in case control  
6 studies, done by examining time to pregnancy  
7 in conditions of unprotected intercourse is a  
8 metric that's been used in a variety of  
9 epidemiologic studies.

10           There are examples of studies of  
11 spontaneous abortion, of course, from the  
12 drinking water. Family, as well as from -  
13 actually, from the pesticide research. And  
14 they may also add important information with  
15 respect to phenotoxicity that might be seen in  
16 a laboratory animal.

17           Just to point out along the way  
18 that there are issues with many of these end  
19 points. For example, the well-recognized  
20 phenomenon that about 20 to 25 percent of  
21 spontaneous abortions are not clinically  
22 recognized because they occur so early in

1 gestation that they can't be counted.

2                   So, once you go through the  
3 thought process here of examining the end  
4 points, then moving to stillbirth, to neonatal  
5 deaths, and then that issue of growth  
6 retardation that is shown in some of these  
7 examples, is a convenient metric for these  
8 analyses because the information is generally  
9 available from the birth certificate. And  
10 that's the reason I ask the question about  
11 linkage, data linkage with the AHS, because it  
12 would be a convenient and rather efficient way  
13 to examine at the early stages of exploration,  
14 potential associations between specific  
15 agrochemicals and outcomes.

16                   So, you could use birth weight as  
17 a continuous variable, you can use the  
18 definitions of "low birth weight" and "very  
19 low birth weight," you can use intrauterine  
20 growth retardation or small for gestational  
21 age directly from birth certificate data, and  
22 pre-term birth defined as delivery before 37

1 weeks of gestation, again, are data sources  
2 and data points that are available to use in  
3 this general category of studies.

4                   It's not, obviously, a  
5 longitudinal prospective study, but the more  
6 efficient and easier studies to do in  
7 epidemiology can in fact address those end  
8 points.

9                   The birth defects work is hazard -  
10 it's a little tricky. It is very tricky,  
11 actually, for reasons that others have  
12 mentioned particularly due to the  
13 heterogeneity of probable pathways and causes  
14 of specific defects or groups of defects.

15                   So, for example, it's very common  
16 for people to look at cardiovascular defects  
17 when, in fact, this represents a heterogeneity  
18 of lesions that may, in fact, have different  
19 etiologic mechanisms.

20                   So, I think just thinking about  
21 these things in a more generic way can help  
22 guide where we should direct our efforts.

1                   And there are examples, in fact,  
2   in the atrazine literature of menstrual cycle  
3   changes with respect to the characteristics  
4   and length of menstrual cycles. Of course,  
5   under-control of the hypothalamic pituitary  
6   access and the gonad, I think, are important  
7   end points to look at, as is age at menarche  
8   in younger women, and age at menopause in  
9   older women, because I think all of those are  
10   informative, again, linked back to the  
11   biological plausibility question and the  
12   mechanism of action issues that have been  
13   raised by the agency, which I concur heartily  
14   are absolutely the right direction to go.

15                  And finally, when thinking about  
16   reproductive end points, one shouldn't ignore  
17   the male. I have to say that as probably  
18   about 50 percent of the equation. And, in  
19   fact, I think the recognized or the usually  
20   quoted statistic is that about half of the  
21   infertility that occurs in human couples is  
22   the male side of the partnership as opposed to

1 the female side.

2 And there are even, for example,  
3 studies that have explored the relationship  
4 between atrazine and semen characteristics  
5 that are important to bring into a weight of  
6 the evidence analysis.

7 CHAIR HEERINGA: Thank you, Dr.  
8 Reif.

9 Dr. Bailar.

10 DR. BAILAR: I don't have much to  
11 add. This will be relatively short.

12 CHAIR HEERINGA: Get your mic  
13 there, John.

14 DR. BAILAR: The EPA report should  
15 first acknowledge that ecologic studies, and  
16 to some extent retrospective epidemiologic  
17 studies, are inherently weak vehicles for  
18 quantitative estimation.

19 This is not a criticism of such  
20 data which may have considerable strengths in  
21 other ways such as generating hypotheses,  
22 supporting smaller and inconclusive data of

1 stronger inherent character providing floors  
2 to the size of some effect in support of  
3 legislation or regulation and so forth, but it  
4 is important that EPA not overstate the  
5 strength of such work in the interpretation  
6 and analysis of problems.

7           That said, there is a spectrum of  
8 strengths. Not all such studies are equal.  
9 Look for some of the following things: A  
10 defined population base, whether the  
11 population base has grown as narrowly as  
12 compatible with substantial exposure, that is,  
13 don't dilute possible evidence of real  
14 problems by including persons with little  
15 exposure, except maybe in dose-response  
16 analyses when dose groups are compared, look  
17 for estimated proportion of problems reported,  
18 accuracy and completeness of diagnosis, the  
19 quality and completeness of data known on  
20 unknown or suspected confounders and effect  
21 modifiers, the quality of exposure data.

22           I'm not saying here as much as it

1 might appear. I want to know whether the  
2 investigators have well-defined categories and  
3 whether exposed persons are classified  
4 correctly under whatever scheme the  
5 investigators have chosen, and do not try to  
6 reduce this to a checklist.

7                   There will be too much variation  
8 from problem to problem so that thoughtful  
9 interpretation by the best epidemiologists  
10 available will remain necessary.

11                   CHAIR HEERINGA: Thank you, Dr.  
12 Bailer.

13                   Dr. Portier.

14                   DR. PORTIER: Knowing that my  
15 colleagues would do a much better job of  
16 listing a lot of the details, I'm going to  
17 come back up and I'm going to give you some  
18 general criteria that I've extracted from the  
19 literature. And there will be some references  
20 in there as well.

21                   I'll start with a quote I came  
22 across which I thought is pretty good, a

1 pretty good summary. It says good, quality  
2 epidemiological studies are those with sound  
3 methodology, lack of bias, long enough follow-  
4 up times to observe a health effect - this was  
5 a carcinogenic study. So, I've replaced  
6 "health effect" with "carcinogenic" - a health  
7 effect response, adequate exposure information  
8 and dose-response information.

9           Before a lack of health effect can  
10 be inferred, it's essential that the exposures  
11 be of substantial duration and intensity, and  
12 that the number of exposed persons be  
13 reasonably large.

14           One of the things that this brings  
15 to mind is that a good epi study - most epi  
16 studies aren't good at looking at very rare  
17 events. They're much better for events that  
18 you can get cases on. So, it's not going to  
19 be looking for those really rare health  
20 conditions.

21           And then I listed a set of nine  
22 general criteria, which a lot of which have



1    been talked here. And I'm just going to read  
2    these, because it summarizes it. Again, a lot  
3    of this was extracted from a paper by Swaen in  
4    2006 in Human and Experimental Toxicology, but  
5    I've kind of added and enhanced it.

6                    So, the study design should be  
7    appropriate to the study objectives, and  
8    should take into account the time frame of the  
9    exposure to health effect relationship.

10   That's number one.

11                   Number two, and appropriate  
12   comparison groups should be used. Appropriate  
13   matching. We've talked about that.

14                   If applicable, measures of  
15   exposure should be corrected for known  
16   confounding factors, including concomitant  
17   exposures.

18                   Now, a big one. The sample size  
19   of a study should be such that if in reality  
20   there is an association between a certain  
21   exposure and health effect, the study will be  
22   capable of distinguishing this effect from a

1 no-effect situation on a statistical  
2 significance level.

3 In other words, it has to have  
4 sufficient statistical power for identifying  
5 meaningful differences. A negative study  
6 can't be interpreted if one doesn't know the  
7 probability the study can detect an effect if  
8 it is present.

9 In other words, we talked a little  
10 bit about negative studies, but the key  
11 component about understanding a negative study  
12 is understanding the sample size that's  
13 involved, because that tells me whether I  
14 missed a big difference or not simply because  
15 I didn't look at enough people.

16 The fifth thing is the appropriate  
17 statistical analysis is used. Use statistical  
18 estimation and testing methods which account  
19 for multiple comparisons when multiple health  
20 outcomes are examined.

21 I think all of you know the  
22 dangers of exploring without taking into

1 account the fact that every time you do a  
2 test, there's a chance you're going to be  
3 wrong and that it's not significant.

4           The quality and reliability  
5 exposure measurements must be assessed. Three  
6 types of exposure data may be used. Actual  
7 data, and there's kind of two forms of those;  
8 external, where the external dose is taken  
9 from measurements in the individual's  
10 microenvironment, or an internal dose through  
11 biomonitoring, that's actual data. There's  
12 analogous data where an exposure situation is  
13 used as a surrogate for the actual data. And  
14 then there's, which we haven't talked about,  
15 is predicted exposure data where we're getting  
16 an exposure value from some kind of validated  
17 modeling technique.

18           All of these things have to be  
19 assessed against some kind of actual data to  
20 ensure their predictive ability.

21           We want to avoid the use of  
22 exposure indices that have poor predictive

1 ability. And if an exposure index is used, it  
2 must be validated to the actual data.

3 The exposure measurement must  
4 provide adequate, discriminating power to  
5 detect exposure-related hazard. At a minimum,  
6 that means we need reliable gradations of  
7 relative exposure amounts.

8 So, if you don't have individuals  
9 in exposure categories that relate to some  
10 kind of a scale, you're not going to be able  
11 to get toward the dose-response relationships.

12 Exposure metrics can represent  
13 dose values, for example, average daily dose,  
14 cigarettes per day or some peak dose, it can  
15 represent a duration value like length of  
16 exposure, example, years smoked, combined  
17 together into a cumulative exposure metric.  
18 And I'd like to think of cumulative exposure  
19 metrics kind of like area under the curve  
20 statistics that integrate duration and  
21 intensity, which you talked about in your  
22 document.

1                   A few last things. The quality  
2   and reliability of the health effects data  
3   must be assessed. Medical records typically  
4   have higher value than self-reported health  
5   effects, more recent events of more value than  
6   events that happened a long time ago. And we  
7   just mentioned using state birth and death  
8   registries where there's a quality assessment  
9   of the health record data that comes along.

10                  Temporal variability, spatial  
11   variability and variability due to individual  
12   behavior as it relates to exposure, should be  
13   accounted for in the study. It should have a  
14   sufficiently long observation period with  
15   respect to the expected latency health  
16   effects.

17                  And then in case control  
18   retrospective studies, completeness of case  
19   ascertainment should be the same between the  
20   exposed and the non-exposed group, that  
21   relates to high power and fair comparisons.

22                  And I think those criteria really

1 work for both retrospective studies and  
2 ecological studies. They're kind of general  
3 things. Although, most of the ecological  
4 studies are going to be unable to meet some of  
5 these criteria.

6 Now, I can't let Dr. Bove's  
7 statement about statistical significance go  
8 unchallenged. So, my question is how do we  
9 know something is significant and needs  
10 focusing on if we don't pay attention to the  
11 statistical significance or confidence  
12 intervals.

13 So, we constantly say things like  
14 an odds ratio of four, and you say oh, that's  
15 great, but the confidence interval starts at  
16 .5 and goes to 27. And I don't really know  
17 what that means anymore unless I look at the  
18 statistics and take into account the sample  
19 size and the power of the study that we  
20 started with.

21 One can, though, compute and use  
22 the probability that the odds ratio is greater

1     than a particular value in the decision  
2     process. So, kind of the - if you, you know,  
3     statisticians kind of less emphasize the point  
4     estimate and more emphasize the interval  
5     estimate or the probability of an event  
6     occurring.

7                     So, it might be that when you're  
8     factoring this into the risk assessment, the  
9     chance that the relationship could be high,  
10    that chance is significantly high, you can  
11    factor that into the decision process.

12                    There's still a good chance that  
13    you could be wrong if the confidence interval  
14    includes one, but I'll go part of the way with  
15    Dr. Bove on this, but not all of the way.

16                    I think I'll stop at that point.

17                    CHAIR HEERINGA: Thank you, Dr.  
18    Portier.

19                    Dr. Bove, I think I was  
20    interested, too, in these points of view. And  
21    this is, I think, very important. I and others  
22    here have been on other advisory panels and

1 advisory boards that were chemical specific,  
2 and the wide array of epidemiologic data - I'm  
3 thinking of arsenic now. And in the end,  
4 there was a clear difference of opinion on the  
5 expert panel as to how to utilize some of  
6 these data that clearly the power wasn't  
7 adequate to necessarily detect true values of  
8 interest, but the indications from the data  
9 themselves or of trends, of comparable odds  
10 ratios across studies.

11 Dr. Bove, is that sort of the line  
12 of thinking you were saying that if you see  
13 trends and results across studies even though  
14 individual studies may not be adequately  
15 powered, as Dr. Portier suggests?

16 DR. BOVE: Well, that's true, too,  
17 if you look at several studies and they're all  
18 seeming the same direction, but none of the  
19 studies had the statistically significant  
20 finding. That's one issue.

21 But yes, you know, I think that -  
22 but that is part of why I'm saying what I'm



1 saying. In any particular study, you can  
2 always do a whole p-value function curve and  
3 see what alternative hypotheses are probable  
4 based on that or at least more likely than  
5 others.

6 I mean if you're interested in  
7 doing that, that's fine. But if you use  
8 several confidence intervals, for example,  
9 nested confidence intervals, the p-value  
10 function really interpret the data and that's  
11 fine.

12 If you're just going to say if  
13 it's in or out of the lower limit of a 95  
14 percent confidence interval, to me that takes  
15 that art away from interpretation. We've  
16 heard that conversation this morning.

17 And it leads you to do things that  
18 would actually lead you astray such as  
19 ignoring findings that after several studies  
20 seem to pan out. I mean there are examples  
21 actually I can point to today from the studies  
22 under review if we want to go through, you

1 know, and I'll do that later maybe.

2 But this is a big debate in the  
3 field. The issue about multiple comparisons  
4 is a big debate. A lot of epidemiologists  
5 come on both sides of that issue. And some  
6 say that instead of worrying about the p-  
7 value, if there are ways to adjust the point  
8 estimate itself through some kind of Bayesian  
9 method, that's fine. But, again, I don't know  
10 if we can resolve this here.

11 Again, I think that what's  
12 important is that statistical significance is  
13 not one of Hill's viewpoints, although he does  
14 refer to it in the paper. And I think that of  
15 course someone can make that claim that if  
16 it's not statistically significant, I'm going  
17 to ignore it, but I don't think that that's a  
18 very good method of interpreting data.

19 CHAIR HEERINGA: Dr. Portier.

20 DR. PORTIER: I do agree with you  
21 that when you read the literature, oftentimes  
22 the researcher excludes from the discussion

1 things that they thought were not  
2 statistically significant. And I really think  
3 they should put it all in there.

4 I'd rather see all of them, even  
5 the non-significant ones, because you - you're  
6 absolutely right.

7 The other thing that EPA hasn't  
8 asked us about in this document is a meta-  
9 analysis when we start putting these things  
10 all together. And that's when you start  
11 seeing those things that are near significant,  
12 near significant, near significant. But then  
13 when we put a number of studies together to  
14 get a broader range of exposures, the trend  
15 all of a sudden shows up. Right?

16 They may be insignificant in the  
17 smaller studies. But in the broader view, all  
18 of a sudden it becomes significant. And you  
19 won't notice that if those things are not  
20 provided, and I agree with you on that.

21 I think non-significant is not a  
22 reason to not talk about it, to not put it

1 into the - I would agree on that.

2 CHAIR HEERINGA: Thanks. Dr.

3 Bailar.

4 DR. BAILAR: A couple of footnotes.

5 Generally, I'd like to encourage EPA to

6 minimize the use of p-values and go for

7 confidence bounds wherever you can calculate

8 them or pick them out of the literature.

9 They're just so much more informative.

10 Among other things, they take care

11 of the problem of small samples. Confidence

12 bounds turn out to be much wider, and

13 everybody can see that you didn't have much

14 chance of binding an effect with this kind of

15 study, this kind of design, this kind of

16 sample.

17 Furthermore, we're used to seeing

18 confidence bounds at a particular probability

19 level, but it's not difficult to put in more

20 than one level. You can show ten percent

21 bounds, five percent, one percent on the same

22 figure, the same set of bars, and sometimes

1 that can be informative.

2 The other footnote, Dr. Portier  
3 went through a very nice catalog of the  
4 sources, kind of exposure information. To  
5 that I would central monitors. That may not  
6 be a big issue in pesticides, it might come up  
7 once in a while if you're dealing with very  
8 broad, airborne contaminants, but it is  
9 important in some other kinds of analyses that  
10 EPA is interested in.

11 CHAIR HEERINGA: Thank you, Dr.  
12 Bailar.

13 And I saw a number of people  
14 nodding at the comment on the display and use  
15 confidence intervals to reflect uncertainty.

16 In my view, that's the world that  
17 I live in. A simple one star, two star, three  
18 star, no star doesn't provide you the type of  
19 information that you need to make an art out  
20 of this.

21 So, I think we're converging a  
22 little bit here. Does anyone else have

1 thoughts on that?

2 But I think that's important  
3 because it reflects how people present results  
4 in scientific papers and in presentations.  
5 And I think particularly in this domain seeing  
6 those confidence bounds on relevant statistics  
7 is very, very important.

8 Dr. Gold.

9 DR. GOLD: I would support that you  
10 get more information by the confidence  
11 intervals, but I'd also point out that there's  
12 nothing magical about .05 either. It was  
13 totally arbitrarily picked.

14 And so also looking at 90 percent  
15 confidence intervals, for example, it's often  
16 done in occupational studies. And as, in my  
17 training, one of the statisticians point out  
18 most of us make decisions based on values much  
19 greater than five percent.

20 So, I think that's, I think, where  
21 the comment about not adhering so stringently  
22 to statistical significance comes up, because

1 you make decisions in life based on much  
2 higher p-values.

3 CHAIR HEERINGA: We should all have  
4 been born with a table of T statistics in our  
5 heads, and we would have walked back and forth  
6 between the two.

7 Other comments on this particular  
8 item?

9 I guess we'll move on. I'll turn  
10 to Dr. Lowit. Any questions? Lieutenant  
11 Niman, we would like to read the next question  
12 into the record, please.

13 LTJG NIMAN: Question 2.2, ecologic  
14 and retrospective epidemiology studies are  
15 particularly useful in identifying new  
16 hypotheses about the human health effects of  
17 pesticide exposure and may confirm the human  
18 relevance of findings from experimental animal  
19 studies. However, these types of studies do  
20 not typically include robust characterization  
21 of exposure and they do not address  
22 confounding factors as well as prospective

1 studies. Although there may be exceptions,  
2 generally, ecologic and retrospective  
3 epidemiology studies are generally not  
4 sufficiently robust for use in quantitative  
5 risk assessment, i.e., for use in deriving  
6 point of departure or in quantitatively  
7 informing extrapolation factors. In light of  
8 the strengths and limitations of the ecologic  
9 and retrospective studies, please comment on  
10 appropriate ways to use these types of  
11 epidemiology studies in risk assessment/risk  
12 characterization or their utility in problem  
13 formulation.

14 CHAIR HEERINGA: Dr. Greenwood is  
15 our lead discussant.

16 DR. GREENWOOD: Well, I looked at  
17 this against the background of the proposed  
18 changes towards the National Research Council  
19 move towards looking at pathways and so on,  
20 and I think it's going to be a long  
21 transitional period. And I think that you're  
22 going to need to continue looking at any sort



1 of information that you can get in the move  
2 towards the new paradigm for risk assessment.

3 And I think the epidemiological  
4 studies certainly have potential to provide  
5 important information in looking at your  
6 assessment, the assessment of other people.

7 Certainly they could inform  
8 experimental toxicological end points, and it  
9 could also be useful in making people aware of  
10 possible lesions that they haven't predicted  
11 or taken into account in the absence of, say,  
12 of a mode-of-action study.

13 But like all information, they  
14 really do need to be scrutinized very  
15 carefully just in the same way that  
16 toxicological data need to be scrutinized very  
17 carefully to make sure that the design and  
18 analysis and so on, the way they do the  
19 methodology, are appropriate.

20 There is a difference, though,  
21 because for a lot of toxicological assays,  
22 there are standards available. There are

1 definite and well-defined methods for  
2 demonstrating the validity of the assays, and  
3 they can only be done by people who are  
4 accredited to do some of those assays.

5           So, a lot of the routine assays,  
6 toxicological assays, have been validated.  
7 And I think there's a real need for looking at  
8 developing some sort of framework, and I think  
9 already Dr. Bove has already hinted at or  
10 given some ideas for looking at the validity  
11 of epidemiological studies.

12           It makes an enormous difference,  
13 and I always call it the field of analytical  
14 chemistry where at 20 years ago the analyses  
15 you got from laboratories were by and large  
16 very unreliable. And that was shown by the  
17 early interlaboratory trials.

18           And over the last 20 years,  
19 validation protocols have been developed and  
20 the reliability of analytical data now is  
21 very, very much improved. It's a totally  
22 different field from what it was 20 years ago.

1                   And I think that in your document,  
2   you've identified the main difficulties. And  
3   one of them is obviously in the assessment of  
4   exposure and identifying the other factors  
5   which might be correlated with that exposure  
6   or associated with it.

7                   It's very, very difficult to  
8   estimate exposure even under good conditions.  
9   If you look at some of the studies where -  
10   biomonitoring studies, people have had great  
11   difficulties. Even when it's on an individual  
12   basis, they've taken the urine, all blood  
13   samples, done the analysis, and then try to  
14   link that to the exposure scenario, and it's  
15   not as easy as you might think. And often  
16   there are large uncertainties associated with  
17   it. The confidence intervals are very wide.

18                  I think that the estimates of  
19   exposure that we've seen in some of the  
20   studies really would not pass any validation  
21   mechanism. We'll come up to that perhaps in  
22   the next question.

1                   And the other problem is that  
2   yesterday I think someone was saying well, why  
3   not stick to the high dose with worker  
4   exposure, but actually that doesn't cover a  
5   huge proportion of the population. And that  
6   certainly wouldn't cover, for instance,  
7   spouses and the offspring of workers, let  
8   alone the general public.

9                   And certainly that source of  
10   contamination through people taking home  
11   contaminated clothing and so on is well-  
12   documented for the asbestos cases, for  
13   instance, where spouses were exposed to  
14   asbestos from the clothes of their spouse.

15                  So, none of this sort of should  
16   happen, really, if there's good practice, but  
17   contamination - there isn't always good  
18   practice. There are failures and  
19   contamination can occur, which adds an extra  
20   uncertainty when we're dealing with  
21   epidemiological studies.

22                  I think rigorous estimates of

1    biomonitoring are difficult to achieve.    And  
2    I do feel that there's this scope in the way  
3    that epidemiological studies are looked at in  
4    future and maybe trying to do some validation  
5    of the exposure or maybe insisting on some  
6    validation, external validation of the  
7    exposure data.

8                    But it's not easy even when you  
9    have urine samples, because - there's a pilot  
10   study by Bartlett I think in 2007, where  
11   people traditionally look for atrazine capture  
12   rates in urine, and use that as a measure of  
13   exposure.    But actually what he found was that  
14   something like 70 to 80 percent of the  
15   exposure was due to a couple of metabolites,  
16   the diamino chlorotriazine and deethyl  
17   atrazine, which were the predominant compounds  
18   in the urine and a much better indicator of  
19   exposure as those compounds have been thought  
20   to be active in their own right.

21                    So, the atrazine recapture is  
22   actually underestimating the exposure.    So,

1 it's very, very difficult to get a good fix on  
2 that. And I think that if we're to take  
3 epidemiological studies seriously, this aspect  
4 really needs some sort of validation.

5 I think the other problem is that  
6 as with experimental toxicology, it's a big  
7 problem for the field, that there's a tendency  
8 to look at each compound in isolation, because  
9 that's the way we did the toxicological  
10 testing, that's the way we think about it.

11 Actually, that is a chemical soup  
12 that anybody's who's into water monitoring  
13 knows just how many compounds there are in  
14 that soup, and it's more than we can measure  
15 realistically.

16 So, it is difficult with any  
17 study, to actually understand whether that one  
18 compound on its own is the problem or whether  
19 it becomes a bigger problem or a smaller  
20 problem in the presence of other contaminants.

21 And somehow or another I think  
22 this needs to be taken into account when

1 assessing the exposures which are used in  
2 epidemiological studies.

3                   And it's not just the pesticides.  
4 You've got to think in terms of the huge  
5 numbers of industrial chemicals,  
6 pharmaceuticals, household product components,  
7 personal care products and components. And  
8 some of them even vary on a seasonal basis.  
9 Sunscreen components in lakes in Switzerland,  
10 big problem in summer. Not in winter, because  
11 it's too cold to swim and not too much sun,  
12 but they are a problem.

13                   And these sorts of things often  
14 are forgotten about when people are  
15 concentrating on one group of compounds which  
16 are of known biological activity.

17                   Given all of these reservations, I  
18 think that epidemiological studies do have the  
19 potential to make a significant contribution  
20 to particularly risk characterization, and in  
21 some cases risk assessment, in a number of  
22 areas.

1                   And I think that one of the areas  
2   is the identification of potential health  
3   problems which may not have been previously  
4   considered as being associated with exposure  
5   to pesticides.

6                   And I think vigilance is something  
7   which needs to be maintained. And it could  
8   help in that case, to prioritize research  
9   efforts. But there may be opportunities to  
10   look at the validity of some studies in areas  
11   where there have been changes in practice.

12                  So, for instance, in some areas of  
13   Europe now, the use of atrazine is severely  
14   curtailed and it's prescribed for many of the  
15   applications for which it was used previously.  
16   Particularly for maintaining road surfaces and  
17   weed maintenance on those railway embankments  
18   and so on, which really are a very large -  
19   provide a large component of environmental  
20   contamination.

21                  And it might be possible there to  
22   look at an effect, if it's a seasonal effect,



1 see whether it was there before the removal of  
2 the compound, and after the removal of the  
3 compound not just for atrazine, but for the  
4 compound.

5 But I think the big contribution  
6 that epidemiological studies might be able to  
7 make is at the problem formulation stage. And  
8 I think as you move towards the new paradigm,  
9 I think it's going to be even more important  
10 that the people in different areas, the  
11 toxicologists, the epidemiological  
12 toxicologists, all actually speak to each  
13 other, the analytical chemists, all people  
14 actually have an input at that stage.

15 And I think certainly it could  
16 inform prioritization of research and maybe  
17 help to inform what sort of internal exposures  
18 people should be looking for on the basis of  
19 observed external exposures.

20 So, I think that providing we can  
21 in the future move towards better  
22 collaboration between disciplines, I think it

1 would be easier to actually provide validation  
2 of some of the steps in epidemiological  
3 studies.

4 I'll leave that there and hand it  
5 over to my epidemiologic colleague.

6 CHAIR HEERINGA: Thank you, Dr.  
7 Greenwood.

8 Dr. Reif.

9 DR. REIF: Yes, thanks. I  
10 commented earlier today about the inherent  
11 dangers of kind of lumping ecologic studies  
12 and what are called retrospective epidemiology  
13 studies. And I think that, again, and I'll  
14 just reiterate that that's probably not a  
15 useful collapse of study designs.

16 I think the question as it's  
17 framed, probably applies pretty well to  
18 ecologic studies. It doesn't apply equally  
19 well to case control studies or historical  
20 cohort studies.

21 I'd just like to give a couple of  
22 examples of, first, one of a historical cohort

1 study that is, I think, a useful discussion  
2 point although it's not about atrazine. It's  
3 about DDT. And then I'd like to talk about  
4 one of the other designs for a moment that's  
5 in the case example.

6           Going back about 20 years ago  
7 there was a small body of evidence that  
8 suggested that accumulation of lipophilic  
9 organochlorine pesticides, DDT and others, was  
10 related to breast cancer risk. And those  
11 original observations were based on biopsies  
12 of fat taken from women with tumors and women  
13 without when fat was available from other  
14 means. And some small case control studies  
15 using that biomonitoring approach found  
16 differences in the concentrations of DDT and  
17 other organochlorines. And that began quite  
18 an effort, actually, to evaluate the role of  
19 organochlorines in breast cancer risk.

20           One of the answers came from a  
21 study done in which sera had been banked from  
22 women about 20 years previously. And I

1 believe it was Nancy Krieger who did this, but  
2 my memory may be faulty, and I'll check on it.

3 But the beauty of it was, and this  
4 is a retrospective design, this is an  
5 historical cohort study, that these sera  
6 available from a fairly large sample of  
7 California women taken over 20 years ago,  
8 could now be used in exposure assessment and  
9 by using registry methods - I forgot what the  
10 ascertainment was specifically, but to then  
11 ascertain those women today. And that is at  
12 the point when the investigators did the  
13 study.

14 So, they had historically faced  
15 exposure data, quantitative using for the day,  
16 sophisticated measurements with levels of  
17 detection that could measure these things in  
18 sera which was kind of new, because prior to  
19 that they had to have a fat sample prior to  
20 the resolution improving.

21 So, it's just an example of here's  
22 a retrospective study, it's just one of those

1 phenomena that we're going to see more and  
2 more because it is becoming more and more  
3 commonplace for epidemiologists to bank tissue  
4 as they do studies. To bank buccal swabs for  
5 DNA, to bank sera for who knows what down the  
6 road as new hypotheses develop.

7               So, it really isn't fair to  
8 because the study is retrospective, as is that  
9 historical cohort study, to sort of say it has  
10 these inherent limitations that are not going  
11 to make it useful for risk assessment.

12              It could be extremely useful, and  
13 that's the example that I'd offer in that  
14 context.

15              The other thing that the question  
16 sort of raises in my mind, has to do with this  
17 surrogate exposure for proximity to fields  
18 where pesticides have been applied.

19              Actually, I've been involved in a  
20 study like this, and I think they are - this  
21 kind of spatial epidemiology using GIS tools  
22 and using data, for example, that's available

1 for specific pesticides in specific locations  
2 where one knows what the application dates are  
3 because of the emergence of the weeds that are  
4 being killed, there are relatively specific  
5 windows of exposure when certain pesticides  
6 will apply.

7           There are also very specific  
8 windows of susceptibility in the development  
9 of the fetus so that it at least conceptually  
10 is somewhat attractive to explore the  
11 potential relationship between the timing of  
12 application of pesticides and specific events  
13 that may be occurring in utero in the pregnant  
14 female. So, this has some - at least some  
15 theoretical appeal.

16           What hasn't happened, which I  
17 think is a worthwhile objective, is for a  
18 validation step to occur to determine whether  
19 or not the women, for example, who live within  
20 500 meters of the edge of a field containing  
21 corn or sorghum at a specific point in time in  
22 the early spring when the pesticides are

1 applied, whether one can find evidence first  
2 of environmental exposure by house dust  
3 sample.

4               So, the whole technology, as you  
5 know from the industrial hygiene field of  
6 exposure assessment, has really improved  
7 recently. And these kinds of validation steps  
8 which are really not that difficult in a study  
9 where one would collect house dust samples and  
10 analyze it for the persistent kinds of  
11 pesticides that are environmentally  
12 persistent, has then the potential of adding  
13 validation to the spatial GIS-based analysis.

14              We went a step further and took a  
15 sample of farms where you had proximity to  
16 fields and you had house dust samples, and  
17 then did human biomonitoring. You would now  
18 bring the exposure assessment closer to the  
19 objective, which is really to get a handle on  
20 what human exposure is.

21              So, I see even the study that's in  
22 the case analysis, is rather crude and

1 certainly can be criticized. That doesn't  
2 mean that the design of considering spatial  
3 analyses using GIS techniques should be  
4 dismissed.

5 In fact, my belief is that it  
6 should be strengthened by enhanced exposure  
7 assessment methods done by industrial  
8 hygienists.

9 So, those are the comments I  
10 wanted to offer. They're not terribly germane  
11 to the question, but the question itself has  
12 some features that are difficult to  
13 conceptualize for me.

14 CHAIR HEERINGA: Thank you, Dr.  
15 Reif.

16 Dr. LeBlanc.

17 DR. LeBLANC: Well, first off I  
18 would agree with the agency that these types  
19 of studies have limited quantitative value in  
20 the risk assessment process. But having said  
21 that, I think they still offer significant  
22 qualitative value that should be considered.



1 I think that the greatest value to  
2 these studies as it relates to the risk  
3 assessment process, is both at the front end  
4 of the process as well as at the end of the  
5 process.

6 And I'm not an epidemiologist.

7 And I'm proud of myself, I suppose, because  
8 the points that I listed as being relevant to  
9 the answer to this question were voiced  
10 precisely by Dr. Greenwood. So, thank you.

11 What I would like to do is just  
12 touch upon some of these points in the risk  
13 assessment framework just to sort of draw  
14 attention as to where the strengths are and  
15 where the weaknesses are to the retrospective  
16 ecological-type studies in this process.

17 As stated by many now, I think  
18 problem formulation is certainly, I think  
19 personally, the best place to place these  
20 studies, the results generated from these  
21 studies.

22 In my mind, they seem largely to

1 be exploratory in nature, but the observations  
2 that are derived from these studies,  
3 nonetheless, can be used to direct hypothesis  
4 setting, as well as directing the analysis  
5 towards testing these hypotheses. And I think  
6 all of that would fit up front in the risk  
7 assessment process.

8 Another thorn in the side of  
9 certainly toxicologists as it relates to risk  
10 assessment is evaluating the risk of toxicity  
11 associated - or hazard of toxicity associated  
12 with chemical mixtures.

13 And the reason it's a thorn is  
14 because there's so much complexity associated  
15 with the process. What chemicals do we use in  
16 our assessment, what concentrations of each  
17 chemical do we use in our assessments? And  
18 oftentimes toxicologists will simply throw  
19 their hands up and leave it to someone else to  
20 worry about.

21 But I think there's certainly  
22 potential that these ecological retrospective

1 studies can provide insight into exposure to  
2 environmentally relevant mixtures of chemicals  
3 particularly in an agrochemical setting.

4 And as such, effects that are  
5 discerned under those particular situations,  
6 might be again used in a hypothesis setting  
7 that the results could perhaps run through the  
8 weight of evidence framework to establish the  
9 degree to which causality can be associated  
10 with the mixture, and then provide guidance.

11 The information itself can't be  
12 used, I don't think, in the risk assessment.  
13 They can provide guidance to animal studies  
14 that would be directed towards relevant  
15 exposures to chemical mixtures.

16 Moving on to the exposure  
17 characterization process, it seems that  
18 exposure characterization is inherently a  
19 weakness of these studies. So, I would  
20 suggest that perhaps the utility of these  
21 types of studies in exposure characterization  
22 is limited, but I'll get back to that in a

1 second.

2                   Moving on to hazard  
3 characterization, there are certainly  
4 limitations. And the limitations relate to  
5 the effect that we have a lack of  
6 understanding of exposure in these studies.

7                   And without quite knowing what the  
8 exposure is, it's hard to ascribe hazard of  
9 toxicity associated with the exposure, but  
10 nonetheless they can be cooperative in nature.  
11 They can be used to look back at the animal  
12 studies and see if there's concordance, if  
13 there's consistency between effects observed  
14 in human populations that have been exposed  
15 and the animal studies.

16                  And also, and we touched upon this  
17 many times, they can be used to identify  
18 hazards that are unique to humans that perhaps  
19 we missed in the animal studies.

20                  Exposure characterization and  
21 hazard I would argue are sort of both weak  
22 areas that these studies may have limited

1 value. However, I don't think we can - I  
2 think we still need to keep a perspective of  
3 the fact that consistency in observation among  
4 these studies may be very informative to the  
5 exposure characterization and hazard  
6 characterization process.

7 That is, we may see something in  
8 an ecological study and say well, based on  
9 that study alone because of the lack of  
10 control or recognition of mitigating factors  
11 or lack of understanding of exposure, we can't  
12 make any judgments. But if we consistently  
13 see that response, that effect among many of  
14 these studies, then I think that is very  
15 informative and that should be taken into the  
16 risk assessment process.

17 And then lastly the risk  
18 assessment, I think that these studies can be  
19 used to assess the validity of the risk  
20 assessment, that is, sort of looking back and  
21 seeing whether the judgments that have been  
22 made in the risk assessment are reasonable

1 based upon what we're seeing in exposed  
2 populations.

3 And they also can be used to  
4 provide guidance in risk management, that is,  
5 in situations where the use of material has  
6 been curtailed or perhaps regulations have  
7 been lessened.

8 One can look at responses and see  
9 if there's concordance, if the expectation is  
10 reached and can provide confidence to the risk  
11 management, or alternatively can provide  
12 guidance to appropriate risk management.  
13 That's all.

14 CHAIR HEERINGA: Dr. Bove.

15 DR. BOVE: Looking at this  
16 question, I thought it was rather negative and  
17 pessimistic. And I think that it would help  
18 if the EPA would look at actual risk  
19 assessments that have been performed by your  
20 agency both in draft form and in final form,  
21 and see how human data were used.

22 And I'll give you a for instance.

1 An early draft of the trichloroethylene risk  
2 assessment utilized a couple of occupational  
3 studies and a New Jersey drinking water study  
4 which I was involved in and actually did the  
5 exposure assessment for. And I can tell you  
6 that the water data in the New Jersey study,  
7 and the water data in the Indiana study,  
8 roughly about the same.

9 In the Indiana study, you have a  
10 lot of measurements during the growing season  
11 and hardly any the rest of the year. In New  
12 Jersey you had - if you have a contaminated  
13 system in any system that was a little bit  
14 above the MCL, the New Jersey Department of  
15 Environmental Protection went after them and  
16 made them test quite regularly so that for the  
17 contaminated systems you actually had quite a  
18 bit of data, sometimes monthly, over a three,  
19 four-year period.

20 Anyway, the point I want to make  
21 is that the early draft of the TC risk  
22 assessment used both occupational studies and

1 this New Jersey drinking water study,  
2 calculated the cancer potency for that,  
3 compared it to the animal data, and all the  
4 potency ranges sort of lined up nicely.

5 So, even with data this poor - I  
6 hear all this about how poor this exposure  
7 data is, you know. It's not that poor. Okay?  
8 It's not perfect, it's not great, but it can  
9 be used.

10 My feeling is that instead of  
11 asking the question this way - or better yet,  
12 the best thing the EPA could do is actually go  
13 and look at how health data is being used,  
14 because it's being used. There's no question  
15 about it. It's being used in every part of  
16 risk assessment, including risk  
17 characterization.

18 And maybe looking at those studies  
19 that are used for risk characterization, that  
20 is used for problem formulation and so on and  
21 so forth, you get a sense of what quality data  
22 is being used and how far you can push epi



1 data, because you can push it quite a great  
2 deal.

3 We push animal data, so we can  
4 push epi data as well. So, that would be my  
5 recommendation.

6 CHAIR HEERINGA: Dr. Gold.

7 DR. GOLD: I have very little to  
8 add. I'm just going to make two really quick  
9 points.

10 I think ecologic studies have  
11 significant limitations and we've voiced  
12 those. So, I think they are largely useful  
13 and one could say arguably more useful than  
14 incident data, for suggesting hypotheses for  
15 future well-designed studies so that they can  
16 help drive the research agenda, they can help  
17 in the problem formulation, and they can also  
18 help in examining the consistency of findings  
19 across studies, including ecologic studies.

20 And then in terms of retrospective  
21 studies, I too find this sort of a very  
22 pejorative way of framing the question. I

1 think they really can be quite useful in many  
2 circumstances that my colleagues have already  
3 outlined.

4                   So, I would just say that they can  
5 help provide insights into future analyses as  
6 well. And, again, help identify gaps, help  
7 drive the research agenda, help in the problem  
8 formulation and help generate better research  
9 in the future to overcome some of the  
10 shortcomings of previous studies. That's all  
11 I want to say.

12                   CHAIR HEERINGA: Thank you, Dr.  
13 Gold.

14                   Other members of the panel that  
15 would like to weigh in on this particular  
16 questions?

17                   Dr. Chambers.

18                   DR. CHAMBERS: I'd like to pick up  
19 on a comment that was made by a couple of the  
20 panelists a minute ago. Dr. Greenwood and Dr.  
21 LeBlanc both mentioned the mixtures issues.

22                   This is a generic question not

1 toward any particular risk assessment, and it  
2 kind of brings to mind the chlorpyrifos  
3 discussions from several months ago in an SAP  
4 where there was some human epidemiology data  
5 on chlorpyrifos, but there were also two other  
6 anti-cholinesterases in the people at the time  
7 or in the households and everything.

8           And it troubles me if compounds  
9 are known to have the same mechanism of  
10 action, and yet the effects are attributed to  
11 just one of a mixture of several that have the  
12 same mechanism of action. That doesn't seem  
13 valid to me.

14           That was sort of brought up a few  
15 months ago when we talked about chlorpyrifos,  
16 but it would be valid for any case where the  
17 mechanism of action is known and you've got a  
18 mixture of several compounds that have the  
19 same mechanism of action.

20           Trying to sort out in a  
21 quantitative sense, the effects due to any one  
22 component of the mixture, I think, would be

1 very problematical.

2 CHAIR HEERINGA: Dr. Hayton.

3 DR. HAYTON: Yes, maybe just a  
4 small point, and maybe this is obvious to  
5 many, but Dr. Greenwood mentioned external  
6 versus internal dose. And that since exposure  
7 is a central issue, I think we need to keep it  
8 in mind that the external exposure is really  
9 just a surrogate for the internal exposure  
10 which we often don't know.

11 And I'd just like to point out  
12 that even when we know within a population and  
13 think you know about people taking drugs, if  
14 you give a group of people all the same dose  
15 rate, you will see internal exposures that  
16 vary by, say, a factor of ten pretty commonly.

17 So it introduces, I guess, a foggy  
18 lens between what we think we're measuring as  
19 exposure and what's really going on.

20 CHAIR HEERINGA: Dr. Portier.

21 DR. PORTIER: Ken Portier.  
22 Actually, looking at this question and

1 listening to the discussion, I thought to  
2 myself I wonder if what we're talking about is  
3 actual value, first, versus potential value  
4 for these different study designs.

5           Is it the fact that we like - we  
6 think that perspective studies are more  
7 valuable mainly because they're more complex  
8 and more expensive to do, and therefore we  
9 invest more intellectual capital in those  
10 studies, more time and effort. And, hence, we  
11 get better data in the long run.

12           Whereas if we were able to kind of  
13 invest the same intellectual/capital in a  
14 retrospective study, we could get almost the  
15 same thing.

16           There's this perception that  
17 ecological and retrospective studies are,  
18 quote, cheap. So, they're easy to do. But  
19 maybe we should try to change that and say  
20 these things could be very useful if we spend  
21 the time on it, because we have examples of  
22 retrospective studies that have very useful

1 information. Those are the ones where they  
2 spent the time and put the effort in.

3 So, I don't know if it's the study  
4 design itself that gives us the value for the  
5 risk assessment. It's something else. It's  
6 what scientists invest in those things.

7 Which for the agency means you  
8 need to be thinking about how to encourage the  
9 kind of retrospective studies that garner  
10 those resources to give you those kind of  
11 answers. That's a tough one.

12 CHAIR HEERINGA: Dr. Lowit, are you  
13 satisfied at this point to move on?

14 Okay. I'd like to move on to  
15 Question Part 2.3. That could be read into the  
16 record, Lieutenant Niman.

17 LTJG NIMAN: Question 2.3, the  
18 atrazine case study, Case study A, provides  
19 specific examples of ecologic and  
20 retrospective epidemiology studies. Please  
21 comment on OPP's reviews of the studies  
22 discussed in Case study A. In your comments,

1 please provide specific feedback on the OPP's  
2 descriptions of each study design, exposure  
3 assessment, use of appropriate statistical  
4 methods, and ability to address bias and  
5 confounding in addition to other factors that  
6 may be important in the interpretation of  
7 these studies.

8 CHAIR HEERINGA: Dr. Greenwood is  
9 our lead discussant again on this one.

10 DR. GREENWOOD: well, when I look  
11 at this, I guess the question is really  
12 looking for a general approach, looking at the  
13 general approach taken to the analysis of  
14 these various studies.

15 I think looking at this, the  
16 general approach to evaluation seems to  
17 provide a very useful framework, I think, and  
18 covers the important factors that need to be  
19 dealt with.

20 And I think that the descriptions  
21 are good. The descriptions provided of the  
22 designs, I found those very easy to evaluate.

1                   And I think looking at the case  
2 studies that are presented, most of the main  
3 weaknesses have been identified, but I think  
4 maybe more attention could be paid with maybe  
5 looking at them in a little bit more detail  
6 about a number of things.

7                   One is definition of the outcomes  
8 and the number of outcomes being studied. I  
9 won't cover the ground again, because  
10 colleagues have already been through that,  
11 that we're looking at large numbers of  
12 outcomes. We have one in 20, anyway, to be  
13 significant by chance.

14                  And I think the area that the  
15 agency has identified, and I think everybody  
16 around here has identified as one of the major  
17 problem, is looking in maybe a little more  
18 detail at the exposure and exactly how valid  
19 those exposure measurements are made.

20                  I think in the evaluation the  
21 agency has made, they've made a good  
22 assessment, but I think this is one area which



1 really does deserve extra attention because  
2 it's got to be right.

3 And I think one of the things that  
4 people tend to do because analytical chemistry  
5 is so precise these days and you can depend on  
6 it, people tend to take the analyses, this  
7 quality of them for granted.

8 But actually if you're looking,  
9 for instance, at surface water, even drinking  
10 water and you look at the analytical  
11 chemistry, it can provide you with precisely  
12 the wrong answer. And that's nothing to do  
13 with the analytical step, it's to do with the  
14 sampling step.

15 And often, for instance, with  
16 surface waters, the quality of a river can be  
17 very strong. 12 bottles of water a year. So,  
18 how long does it take to fill a bottle? 30  
19 seconds? So, you're looking at about six  
20 minutes out of a year that are being sampled.

21 And I know from work that we've  
22 done and certainly work from people in

1 Switzerland looking at rivers, that when we  
2 get a rain event, levels of pesticides can  
3 change from next to nothing up through into  
4 tens or 20 micrograms or higher per liter.  
5 And just as quickly, it can fall.

6               So, depending when you take your  
7 sample, you can see that there's a very low  
8 exposure or a very high exposure, and neither  
9 is actually representative of the real  
10 situation.

11              So, I think you need to bear these  
12 sort of factors in mind to look a little  
13 carefully at some of the data. Drinking water  
14 levels tend to change more slowly because just  
15 of the volumes that are collected and treated  
16 and stored and the time of the flow through  
17 the system.

18              But, again, I think with some of  
19 the exposures with drinking water, you could  
20 in fact end up with some quite flawed  
21 information depending on whether people filter  
22 through carbon filter systems, some people do,

1 the water before they drink it in the house.  
2 So, the filtration and so on, because that's  
3 likely as well to be correlated with  
4 associated demographic factors.

5 So, there are lots of problems  
6 with exposure data, and I think that's  
7 probably one area where I think particular  
8 attention, maybe more attention than was paid  
9 here.

10 But overall I think that the  
11 approach that you took was very reasonable.  
12 And to be fair to some of the authors, they  
13 did actually point out the problems with their  
14 own data.

15 So, I'll leave it there again and  
16 pass it over to colleagues, I think, who may  
17 have some more detailed examples.

18 CHAIR HEERINGA: Dr. Bove.

19 DR. BOVE: I don't know if this is  
20 worthwhile doing or not, because, first of  
21 all, these aren't all the studies that have  
22 been done. There are two Iowa studies, for

1 example. One that's published and one that's  
2 not.

3 But the one that's not published  
4 on birth defects was given to the EPA back in  
5 2000. I personally gave it to you at one of  
6 these panels.

7 So, you don't have the whole  
8 universe. So, that's one thing. So, maybe I  
9 shouldn't even talk about the birth defect  
10 study in this packet because there are some  
11 similarities.

12 Min was also elevated in the Iowa  
13 study. So was heart. If you look at the  
14 table here, there's slight effects for heart  
15 certainly not statistically significant.

16 There are problems with this study  
17 in terms of using this metric of distance.  
18 And it's the only one out there, so I don't  
19 know what else to say. I have no problems  
20 with the way it was interpreted.

21 Why don't we move to the small for  
22 gestational age, because we see two studies

1 that you did have in the packet, plus one  
2 that's referenced by one of the studies, the  
3 Munger study in Iowa which should have been in  
4 the packet, but isn't, and all three of them  
5 have somewhat similar findings.

6 The effect is small, but the  
7 effect is somewhere - in the Iowa state, it's  
8 like 1.8, but the Iowa study evaluated  
9 individual level study and turned it into an  
10 ecologic study, unfortunately.

11 It's not the individual level  
12 study which, you know, if I could have gotten  
13 it and did it, I would have done it for them.  
14 It would have been more informative. But they  
15 didn't, so good luck with that.

16 The other two studies that are in  
17 the packet are individual level studies. The  
18 Villanueva study is not an ecologic study.  
19 It's not analyzed, it's an ecologic study,  
20 exposure assessment is not done at an ecologic  
21 level, it's an individual study, and it's not  
22 negative either.

1                   Actually, the stronger effect if  
2   you look at Table 2 in that study, was for  
3   pre-term birth which they don't even evaluate  
4   at all on their paper. The researchers don't,  
5   and the EPA doesn't.

6                   You have actually an exposure  
7   response. You have a medium exposure. You  
8   get a 1.22 odd ratio. And for the high, you  
9   get 1.93. And the 1.93 is pretty high  
10   compared to all the other odds ratios you see  
11   in the paper.

12                  Then you turn to the - another  
13   table in the paper. Let me see if I can find  
14   it myself quickly here. What you see is  
15   actually ver similar between pre-term birth  
16   and small for gestational age.

17                  For pre-term birth looking at the  
18   first trimester and during the growing season,  
19   they have an odds ratio of 1.36. For small  
20   for gestational age in the third trimester  
21   during the growing season, odds ratio of 1.37.  
22   You couldn't get that much closer with the

1 two, but the difference is one is  
2 statistically significant and one is not. And  
3 that's just a numbers problem, okay, but  
4 pretty much the same effect.

5 What's interesting is we don't see  
6 much in the next study with pre-term birth.  
7 And to tell you the truth when I've looked at  
8 pre-term birth and the kinds of exposures I've  
9 looked at, granted they're not pesticide  
10 exposure, I usually don't see much with pre-  
11 term birth either.

12 But still, I think if you want to  
13 interpret the Villanueva study, first of all  
14 it's an individual level study. Secondly,  
15 there is an effect both with pre-term birth  
16 and small for gestational age. And third,  
17 it's not a big effect, is the three things.

18 Now, if you go to the next study,  
19 which is the Indiana study, which has a better  
20 drinking water exposure assessment because  
21 they had more data, okay, and there what we  
22 see - do I have all the tables in here? I'm

1 not sure if all the tables are in this thing  
2 or not.

3 But, anyway, when they looked at  
4 first month for pre-term birth, they see  
5 nothing, basically. So, that doesn't jive  
6 with the previous study.

7 If you look at small for  
8 gestational age, the findings there aren't  
9 very strong either. And if there is a  
10 exposure response, it's very slight.

11 So, how do you interpret that?  
12 Well, we've seen, as I said, two other  
13 studies, the Iowa study and the Villanueva  
14 study, showing slight effects for small for  
15 gestational age. We're talking about pretty  
16 low exposures for the most part. And so  
17 actually those three studies kind of agree  
18 with each other, that is, small effects, small  
19 increases in small for gestational age around  
20 the realm of 1.1 to 1.2 in terms of odds  
21 ratio, prevalence ratio, whatever you want to  
22 calculate here. So, maybe that's how they



1 should be interpreted.

2 Again, my problem with doing this  
3 exercise is that there are - you don't have  
4 Munger's paper here that I would study in the  
5 packet.

6 The amount of work that's been  
7 done in reproductive end points with atrazine  
8 is limited. Okay. It's not as robust as some  
9 of the other chemicals.

10 What is more robust and what I  
11 would like to have seen in this packet, we're  
12 going to look at epidemiology and the role  
13 epidemiology plays in risk assessment.

14 I would have been occupational  
15 studies because there are a number of them.  
16 We've asked EPA to look at them in the past,  
17 and in particular non-Hodgkin's lymphoma  
18 studies. And so, again, I'm blessed with -  
19 I'm not sure the value of this exercise - this  
20 doesn't necessarily - it doesn't capture even  
21 the entire realm of reproductive end points  
22 and atrazine. There's some papers that Dr.

1 Reif knows about and put forward to the panel.  
2 And it's not certainly the universe of studies  
3 of human data and atrazine, including the  
4 occupational studies.

5           So, I'm left with just what I  
6 said, that this is a kind of funny exercise,  
7 but I do think it's important again. I'm not  
8 going to say it anymore after this, but when  
9 you look at these studies, certainly look at  
10 the confidence interval. But look at the  
11 point estimate too, and look at the exposure  
12 response that you see in front of you.

13           And don't say that an exposure  
14 response where you see 1.2 and then 1.9 and  
15 say there's nothing there. That doesn't make  
16 any sense. You can say it's a very weak  
17 finding, you can say it's based on small  
18 numbers, but you can't say it's not there.

19           CHAIR HEERINGA: Dr. Reif.

20           DR. REIF: I have very little to  
21 add. I also found it actually quite  
22 frustrating to consider of the six studies

1 that were included in the case study for a  
2 couple of reasons.

3 I understand that the logic was  
4 that these studies have been published since  
5 an interim decision was made by the agency.  
6 I accept that.

7 But on the other hand, the  
8 selection of these six studies certainly  
9 doesn't fit into a weight of evidence  
10 scenario, because the weight of evidence  
11 scenario would dictate that we should consider  
12 all relevant studies and then do triage to  
13 decide which ones might be informative and  
14 which are not suitable because of study  
15 quality issues.

16 So, I had some frustration with  
17 the exercise also, and in particular because  
18 there were no case control studies in the  
19 suite, and there was a preponderance of the  
20 ecologic hypothesis-generating studies.

21 It was just difficult, actually,  
22 to develop in my own mind any sort of a

1 consensus about well, where are the data  
2 taking us?

3 So, I didn't go to the extent that  
4 Dr. Bove did to look for small differences and  
5 very mild increases in the risk assessments,  
6 because the whole strategy here to me was  
7 incomplete.

8 So, that was my frustration with  
9 the case study, and I just think in the next  
10 iteration of course for future meetings if one  
11 is actually going to look at the potential  
12 risks associated with exposure to atrazine,  
13 that this has to be a true weight of the  
14 evidence analysis in which all the literature  
15 whether it's from 1997 or 2007, is brought to  
16 the table in a comprehensive manner.

17 That goes back to the comment that  
18 was made this morning about how do you do a  
19 literature search, what are the parameters of  
20 the literature search, what are the protocols  
21 for the literature search?

22 The same considerations that are

1     used when we select studies for meta-analysis,  
2     they're equally applicable here because that  
3     kind of rigidity and rigor is important, as  
4     you well know.

5                   And I know that there was - that  
6     the agency know that I was torn between the  
7     sort of bi-partite mission here of trying to  
8     get a handle on the use of epidemiology in  
9     risk assessment. And while we're at it, let's  
10    take a look at some atrazine data. But it's  
11    so fragmented that it's really difficult to  
12    come away with, in my mind at least, with any  
13    kind of clear understanding of risk.

14                  CHAIR HEERINGA: Dr. Lowit.

15                  DR. REIF: Let me just add one  
16    thing. I have very little - other than the  
17    point Dr. Bove made about the Villanueva  
18    study, I do think that the reviews of these  
19    studies by the agency are generally quite  
20    good, accurate and complete.

21                  So, as far as those six studies  
22    go, I think the reviews are adequate for

1 certainly the next step.

2 DR. LOWIT: And just to respond to  
3 the comments about a small subset of studies,  
4 we certainly understand it's dissatisfying of  
5 the scientists to see a small slice of  
6 something that you know in your head and in  
7 your heart is very large, complex database not  
8 only the epidemiology side, but there's a very  
9 complex, rich animal database.

10 And our view, you've heard us talk  
11 about the two hats that we're trying to  
12 balance here. And we felt that those six  
13 studies, as Aaron described yesterday, really  
14 encompassed our goal for this case study as it  
15 is for today.

16 We have a need to make September,  
17 which will involve a more complete evaluation  
18 of all of the epi whether it's reproductive  
19 outcomes, birth outcomes, cancer outcomes in  
20 context with the animal database which is very  
21 large and very rich. And those need to be  
22 done in combination as we're proposing the

1 weight of the evidence.

2 But those six studies provide a  
3 sense of some of the things that we're going  
4 to struggle with in the atrazine, but what  
5 they also provide is a spectrum of the things  
6 that we struggle with in these kinds of  
7 studies, period.

8 I mean it's very common for a  
9 study of this six variety to be published  
10 whether it's atrazine or another robust  
11 chemical or something we don't know much about  
12 where we struggle with how to think about the  
13 exposure assessment and the design and where  
14 it fits in characterization versus  
15 quantitation and how that works. And we want  
16 to do it in the most robust way.

17 So, we understand it's  
18 dissatisfying, but we are working very hard in  
19 the background to complete that picture with  
20 respect to atrazine.

21 We're also working very hard in  
22 the background on a lot of other chemicals.

1 And the feedback that we get on both fronts is  
2 important in both of those goals.

3 CHAIR HEERINGA: Thank you, Dr.  
4 Lowit.

5 Continuing with our associate  
6 discussants that have been assigned here, Dr.  
7 Bailer.

8 DR. BAILAR: I did go through each  
9 of these separately and made notes. There are  
10 three common problems before I get to the  
11 individual papers.

12 One is that what I see here is a  
13 reflection of a very common problem in data on  
14 what you could call big problems, substantial  
15 problems. And that is concerns about bias  
16 dominate concerns about randomness.

17 P-values and confidence bounds  
18 deal only with randomness, and my feeling is  
19 that here the p-values and confidence bounds  
20 are of limited significance because of this  
21 underlying concern about bias.

22 The second is that many of these



1 are subject to problems with multiple  
2 comparisons, and I don't think that any of  
3 them really dealt with that head on.

4           The third is that the effects  
5 they're reporting are relatively small, that  
6 is, relative to the size of the background  
7 effect you're looking at small wiggles in  
8 bigger numbers.

9           The first paper by Winchester,  
10 Huskins and Ying first - the size of the  
11 effect is not at all striking. Maybe six  
12 percent variation from low to high with a lot  
13 of possible season related confounders.

14           The peak incidents in terms of LMP  
15 is May to June. The data would be more  
16 convincing if the authors had found a lack of  
17 such a pattern in mothers who had been  
18 drinking groundwater, and they did not look  
19 separately at surface water and groundwater.

20           Also, I could not find any  
21 evidence in what was here, but the authors  
22 suggested for other seasonally changing

1 chemical exposures, nor did they look at  
2 concurrent data from other states where  
3 atrazine exposures are much lower.

4           The data in Tables A2 and A3 I  
5 found to be somewhat troubling. All but one  
6 of the birth defect types was more common in  
7 April to July than in other months. And the  
8 exception, that is nervous - what was just  
9 called nervous, barely fell below our ratio of  
10 unity.

11           About half of the differences were  
12 statistically significant, but what I know  
13 about chemical teratogens, which is not  
14 extensive, most of them simply don't work that  
15 way. They tend to be much more specific and  
16 I take this broad pattern to be some evidence  
17 of a pervasive bias related to some other type  
18 of seasonally changing factor.

19           The authors and EPA here, I think  
20 I mentioned this yesterday, have missed a  
21 potentially useful analysis related to this  
22 and other papers in this group as they've

1 ignored the older literature.

2 The data were not of the same  
3 quality we have now, but state departments of  
4 health, state vital statistics offices have  
5 for decades collected information on birth  
6 certificates about birth defects. And that  
7 might be of some relevance, because a lot of  
8 those data could be used to find out what was  
9 going on before atrazine was in use.

10 The second paper by Mattix,  
11 Winchester and Scherer, first a couple of  
12 minor points. They had a gap in the data from  
13 1990 to 1995 to 2002. That was not explained  
14 in this draft report.

15 Also, they cite some CDC data and  
16 some Indiana data, but I'd like to know how  
17 the CDC data for Indiana correlate with what  
18 Indiana reports. Did they show very much the  
19 same thing? If there is a serious  
20 discrepancy, that needs to be explained.

21 The authors note that the elevated  
22 Indiana rate they report was statistically

1 significant only in three of the years, but a  
2 critical question here is whether statistical  
3 power was great enough to say that an effect  
4 was present or greater in some years than in  
5 others or are we just looking at the effects  
6 of having small numbers of AWDs in each year.  
7 And were there any special features of  
8 atrazine use during the higher incidents  
9 years?

10                   It appears that they didn't figure  
11 A2 were not adjusted for nitrates, and I  
12 wonder if that can be done.

13                   The third paper, I'm again  
14 concerned about multiple comparisons  
15 especially because the confidence bounds on  
16 the adjusted rates for fields of corn with an  
17 odds ratio of 1.22, which was barely  
18 statistically significant, does not match the  
19 ratio for soybean fields, which does not  
20 suggest an effect.

21                   And it's hard for me to see why  
22 atrazine in one kind of field would not have

1 the same overall effect as atrazine in another  
2 field. And rough agreement with the paper  
3 just above the dates of conception were pretty  
4 much the same.

5           The next paper is focused on low  
6 birth weight, pre-term delivery and small for  
7 gestational age rather than birth defects.  
8 These outcomes are not independent, so the  
9 three sets of results may not provide much  
10 more information than any one of them. It  
11 would be worth checking the correlations if  
12 that is possible.

13           They use the geometric mean. It's  
14 not sort of why. If this was because of  
15 skewness in the distribution, that was simply  
16 the wrong thing to do. It's the high exposure  
17 points that concern us, and it's counter-  
18 productive to reduce their impact on the  
19 analysis by using a geometric mean.

20           Only one year is examined, so  
21 possibly year to year patterns could not be  
22 studied. It's an ecologic study with the

1 strengths and weaknesses of such work.

2           The critical number of data points  
3 on exposure is the number of water  
4 distribution units which was not given in the  
5 materials that I have at hand, nor is there  
6 any analysis of possible co-variates  
7 correlated with distribution units such as  
8 ground versus surface water or local  
9 contamination by known sources of toxic  
10 chemicals.

11           The high point is again May to  
12 September, but now this is in terms of third  
13 trimester which puts the peak six months out  
14 of phase with the data on birth defects and no  
15 explanation for this is altered.

16           Table A7 summarizes the results.  
17 Only one of the nine odds ratios was  
18 statistically significant and barely made it.  
19 And further, we do not know what else the  
20 investigators may have looked at or worked on,  
21 so the problems of multiple comparisons come  
22 up again.

1                   And the next paper, I think it was  
2   the last one, roughly 70 percent of the birth  
3   records available to the investigators came  
4   from one community, which raises questions  
5   about selective effects on reporting, how  
6   implied, was Fort Wayne dominant in the data  
7   and were there local confounders.

8                   There's nothing in this draft  
9   report that explains that. It might be in the  
10  original paper.

11                  The exposure data seems to be  
12  quite weak. Estimates are constructed from  
13  sparse data, especially sparse in the winter  
14  months. But the winter months are critical  
15  because in a sense they're basically the  
16  control period.

17                  Weak signals of an effect were  
18  detected for SGA with exposures in the third  
19  trimester and the entire pregnancy, but that  
20  was not found for pre-term delivery, and low  
21  birth weight was not reported in this part of  
22  the analysis.

1           The range of confidence bounds is  
2 smaller for SGA than for pre-term delivery,  
3 though each is comparing roughly a three month  
4 versus a nine-month period, which may be the  
5 result of having substantially more sample for  
6 the entire pregnancy than for the third  
7 trimester, but this different is not explained  
8 in the materials I have here, and the last  
9 paper was not presented.

10           Overall, I would say that what is  
11 presented in this draft report, and I'm  
12 looking only at what's in this draft, seems to  
13 me to be entire compatible with no effect.

14           CHAIR HEERINGA: Thank you, Dr.  
15 Bailer, for the careful review of each of the  
16 papers. And, again, I think in conjunction  
17 with Dr Reif's comments about the quality of  
18 what's presented in the actual document in  
19 describing these studies, I think there are  
20 some things that have been pointed here that  
21 might be added to what you already have there.

22           I'm interested during the break in



1 speaking to someone - the corn/bean thing is  
2 a bit of a puzzlement. And I think it may be  
3 due to economic practices, no-till versus  
4 Roundup Ready beans and things like that when  
5 the atrazine goes on. I don't know if  
6 somebody can provide me a little background,  
7 but I'd like to be educated.

8 The next discussant is Dr. Hayton.

9 DR. HAYTON: Thank you. I read the  
10 Case study A descriptions and the papers of  
11 interest here, and I thought the case study  
12 fairly described the study design. I was  
13 satisfied with that.

14 I thought the assessment of  
15 exposure was acceptable.

16 The third question we were asked  
17 was whether the case study indicated  
18 appropriate statistical methods, and I thought  
19 there that there was an issue that really  
20 there was no judgment call on whether or not  
21 the statistical methods that were in those  
22 papers were adequate or acceptable.

1                   So, if in fact the case study  
2   should have addressed appropriateness, I  
3   thought it did not.

4                   The fourth question had to do with  
5   bias and confounding and other factors, and I  
6   thought those were reasonably well addressed.  
7   One thing that popped out to me, and that's  
8   the - I think it's the second paper. The  
9   Mattix paper where it's mentioned in that  
10   paper that the abdominal wall defect incidents  
11   occurring in the Riley Hospital - it says 279  
12   over the 1990 to 2002 paper - fewer than half  
13   of those were simultaneously identified by the  
14   state registry.

15                  I thought that was kind of  
16   disturbing that the concordance there was so  
17   low. So, I think maybe that needs some  
18   comment. I don't know what to make of that.  
19   Anyway, that was my response to the questions.

20                  DR. BAILAR: Could I comment?

21                  CHAIR HEERINGA: Dr. Bailar, then  
22   Dr. Portier and Dr. Bove.

1 DR. BAILAR: Abdominal wall defect  
2 is sort of a yes/no diagnosis. Probably  
3 somebody was poking at their abdomen, found a  
4 gap between the muscle on both sides that may  
5 be of no clinical significance, whatever. But  
6 one obstetrician doing that consistently with  
7 a high sensitivity to abdominal wall defect,  
8 could account for the whole thing.

9 CHAIR HEERINGA: Dr. Bove.

10 DR. BOVE: That's true. But in  
11 general, birth certificates and birth defect  
12 registry data do not jive very well at all.  
13 And that's because the birth certificate data  
14 is just not a good source of information on  
15 birth defects. It never has been, never will  
16 be. That's why you need to use population-  
17 based birth defect registries.

18 And Iowa does use it in their  
19 studies. These other studies did not. That's  
20 a flaw. That means they're both under-  
21 ascertaining birth defects, and then there's  
22 also disease misclassification of the defects

1 they do have. They may have the disease, they  
2 might have something else, they may not have  
3 it at all.

4 So, this is the problem when you  
5 use birth certificates for these kinds of  
6 studies. They should not be used for birth  
7 defect research. That's why we have birth  
8 defect registries.

9 DR. HAYTON: So I understand why  
10 there's no - or poor concordance there, but -  
11 so, what's the bottom line there?

12 DR. BOVE: Well, in a birth defect  
13 registry, they have to verify the diagnosis.  
14 They get medical records. They confirm it.  
15 Even the passive systems do that. And the  
16 difference sometimes between passive and  
17 active is not that big a difference.

18 One major difference would be some  
19 of the active systems actually go out to a  
20 year, sometimes they go out to several years,  
21 a good birth defect registry, for example,  
22 California's or New Jersey's or some of the

1 other ones that have been around for a long  
2 time. They go out and capture defects that  
3 occur after the child, the infant comes home.

4 Birth certificates, it's just  
5 whatever a person puts down on the  
6 certificate, whatever is recorded at the  
7 hospital. It's a mishmash.

8 I've done this comparison in New  
9 Jersey, for things that you would think that  
10 you would - that would jive. I mean a neural  
11 tube defect, how could you miss it? And yet,  
12 they don't agree and the birth certificate is  
13 often wrong.

14 So, to explain it, I can't explain  
15 it other than the birth certificate is not  
16 meant for that purpose. The birth defect  
17 registry is meant for that purpose, and that  
18 may be the difference right there.

19 CHAIR HEERINGA: Thank you, Dr.  
20 Bove. That's a good observation.

21 Any more comments from members of  
22 the panel on this particular question?

1 Dr. Portier.

2 DR. PORTIER: So, I agree that the  
3 EPA's review of the atrazine case study  
4 examples, I think, was adequate.

5 For the EPA summary, I would have  
6 liked to have seen a comparison of how LOD  
7 observations were handled in each study. We  
8 know that how the LOD observations are handled  
9 can have a major impact on the summary  
10 statistics, on the associated confidence  
11 intervals, and on any of the statistical  
12 testing and modeling that's done.

13 So, they used half detection or  
14 did they estimate the missing data or did they  
15 set them equal to zero, all of the above, none  
16 of the above?

17 What I also found not adequate was  
18 the background for evaluating the study, so  
19 the context into which we went into these six  
20 studies.

21 It's almost assumed that we were  
22 reading these studies kind of with a blank

1 slate, and in my case it was a true blank  
2 slate, and that the studies themselves would  
3 provide us all a background on the health, the  
4 target health effects, that they would provide  
5 us information on the reproductive health  
6 effects from atrazine, that they would provide  
7 information on temporal and spatial aspects of  
8 the reproductive health effects discussed in  
9 the studies.

10               So, a lot of these were not kind  
11 of provided. So, when I read the papers, I  
12 mean you read the papers cold, but then you  
13 want to know is this reasonable or not,  
14 because I didn't have the background context.

15               So, I would have liked to have  
16 known something about low birth weight, SGA,  
17 pre-term births and the general population and  
18 what kind of trends we've seen nationally and  
19 within these target states over the last  
20 hundred years.

21               I mean, we've had birth records  
22 for a long time. Although they're not

1 perfect, some of these states have had birth  
2 registries for 50 years, maybe.

3 And at the same time as I was  
4 reading this, I wondered about things like  
5 well, does the body mass index or the mother  
6 have an impact on any of these outcomes? In  
7 none of these studies did they talk about the  
8 mother's body mass or the mother's weight.

9 They talked a little bit about  
10 health condition, but I didn't know how that  
11 was assessed. And I would think for these  
12 kind of birth defects, things like that,  
13 especially the mother's, quote, condition to  
14 have birth, would have a big effect on these  
15 kinds of outcomes. And I just didn't get that  
16 in the papers, and then I didn't have the  
17 context in the EPA case study.

18 So, I think as you move forward,  
19 you really need to think about the wrapping of  
20 the studies as well.

21 CHAIR HEERINGA: Additional  
22 comments?



1 Dr. Reed.

2 DR. REED: Yes, I'm still curious  
3 about the possibility of exposure to other  
4 triazines and their breakdown products that  
5 are supposed to have mode-of-action on some of  
6 the end points. So, that would be good to be  
7 addressed.

8 CHAIR HEERINGA: Dr. Bove.

9 DR. BOVE: the Iowa research did  
10 look at cyanazine as well as atrazine. So,  
11 they had some data. There's Rathburn  
12 Reservoir. They had some levels of all those  
13 in that reservoir, and they just compared to  
14 people who aren't on that reservoir, is  
15 basically how they did that study.

16 As for your comment, birth  
17 certificates have changed over time. So,  
18 what's recorded on them changes over time too.  
19 So, for example, in trying to do a study of  
20 birth weight at Hanford in the '40s, I  
21 couldn't do it. There was no birth weight  
22 information. There was gestations age though,

1 so we looked at that.

2 Birth certificates also change in  
3 terms of what kind of maternal risk factors  
4 are there. In the early days, they wouldn't  
5 have smoking and alcohol. Now, they do. How  
6 useful that data is, is oftentimes  
7 questionable, but sometimes it captures some  
8 of the smoking, but the alcohol information  
9 usually is not very good at all.

10 There are also other maternal  
11 conditions in the birth certificate, so that's  
12 where all this information is coming from,  
13 right from the birth certificate, and birth  
14 weight is useful.

15 Small for gestational age is a  
16 useful end point because low birth weight sort  
17 of mixes together pre-term birth and - wait.  
18 I'm sorry.

19 Low birth weight is a mixture of  
20 small for gestational age and pre-term births.  
21 I guess it's getting late. And so by looking  
22 at small for gestational age and pre-terms

1     births, we're separating two different  
2     outcomes.

3                     Although, I do think that in the  
4     future, they should also look at the fifth  
5     percentile, not just the tenth percentile. In  
6     my own work, the fifth percentile seems to  
7     show a stronger effect than tenth percentile.  
8     I think tenth percentile is too broad or a  
9     term low birth weight, which is even more  
10    narrow.

11                    But these are useful end points.  
12    The data is there. Oftentimes people look at  
13    these end points not because necessarily  
14    they're biologically plausible, but because  
15    you can look at them. The data is readily  
16    available, and they're looked at for that  
17    reason.

18                    CHAIR HEERINGA: Additional  
19    comments?

20                    Dr. Bailar.

21                    DR. BAILAR: I would not dismiss  
22    the data on birth certificates too quickly.

1 They are full of errors. No question about  
2 it. Birth defects are grossly under-reported.  
3 No question about that.

4 But the critical question is not  
5 whether there are errors, but whether those  
6 errors are differential. Are they more or  
7 less the same in different places? Are they  
8 more or less stable over time?

9 My guess is that even with the  
10 changes in birth certification, that the  
11 errors in the them, the pattern of errors, the  
12 size, magnitude, direction have not changed  
13 rapidly over, say, a period of ten years, and  
14 I am even a bit more accepting of comparing  
15 patterns in different areas.

16 If you see something in one place,  
17 but not in another in the birth certificate  
18 data, I would give that some consideration.

19 DR. BAILAR: Didn't mean to  
20 denigrate birth certificate information. I  
21 use it all the time. I'm just saying that for  
22 birth defects, there's a much richer, better

1 source of data, and that should be used in  
2 studies.

3 CHAIR HEERINGA: Okay. We have one  
4 more remaining part to Question 2, but I want  
5 to make sure everybody is fresh for that one.  
6 So, let's take a 15-minute break and return at  
7 10 after 3:00.

8 (Whereupon, the above-entitled  
9 matter went off the record at 2:54 p.m. and  
10 resumed at 3:14 p.m.)

11 CHAIR HEERINGA: Question 2.4, can  
12 you read that into the record?

13 MR. DAWSON: Question 2.4, in light  
14 of scientific issues discussed in Questions  
15 2.1 to 2.3, OPP requests input from the SAP on  
16 factors to consider when integrating these  
17 studies in the atrazine WOE analysis currently  
18 under development.

19 DR. REIF: I'm Dr. Reif, and I  
20 would like to ask -

21 CHAIR HEERINGA: We had some  
22 feedback from the audience, that they're not

1 able to hear us. So, please pull your mics  
2 right up tight and speak loudly.

3 Dr. Bailar doesn't need to pull  
4 his quite as close, because he's got a big,  
5 booming voice, but everybody else speak  
6 clearly and closely into the mic so that  
7 everybody can hear.

8 DR. REIF: This last question in  
9 the series that deal with Case study A is, I  
10 think, an overview question of how these  
11 particular studies identified by the agency  
12 can be used in the weight of evidence  
13 analysis.

14 And I believe that with the  
15 probable exception of the Indiana study, that  
16 these studies have significant limitations  
17 that are going to make it difficult to do much  
18 substantively to incorporate these particular  
19 epidemiology studies in a weight of evidence  
20 approach to risk assessment.

21 And that's why I was tempted, I  
22 guess, on my own to look for other studies

1 that were relevant to the question, not to  
2 answer the question of whether atrazine causes  
3 or is associated with adverse reproductive  
4 outcomes, but to look for examples of  
5 epidemiology studies relevant to the question  
6 that used other study designs or that used  
7 other methods of exposure assessment that are  
8 more informative when discussing the broad  
9 issue of incorporating epidemiology studies  
10 into risk assessment.

11 So, I went personally outside the  
12 charge a bit and identified a number of  
13 studies, all of which contain risk estimates  
14 for atrazine for a variety of outcomes.

15 And I'll put these of course into  
16 the report with the appropriate references,  
17 but again it wasn't to do risk assessment, and  
18 epidemiologic evaluation of risk for atrazine.  
19 It was to explore the diversity of  
20 epidemiologic approaches, and then to say to  
21 the agency now, if you were to consider, for  
22 example, this cross-sectional study, you could

1 see what the strengths and weaknesses of a  
2 cross-sectional study are and how the cross-  
3 sectional data might be integrated into the  
4 risk assessment.

5           So, the example of a cross-  
6 sectional study is a study by Farr, et al.,  
7 from the American Journal of Epidemiology  
8 published in 2004, which is built on the  
9 agricultural health study. So, it is actually  
10 nested within the AHS, which brings it to an  
11 additional level of relevance. And the  
12 outcome of interest here is menstrual cycle  
13 activity, length, irregularity, etcetera.

14           So, it isn't - the point is not  
15 whether atrazine was associated with aberrant  
16 menstrual cycle activity. The point is to say  
17 here is an example of an epidemiologic study  
18 well done integrating data from the AHS, which  
19 is using the cross-sectional approach, and now  
20 what can we learn from the study with respect  
21 to epidemiology's contribution to risk  
22 assessment.



1                   So, that was the way that I  
2   thought through this after I got through the  
3   six studies and was somewhat disappointed in  
4   the lack of quality for most of the studies  
5   that's been described by other commenters.

6                   There's another I think that bears  
7   discussion, and that is just as an example  
8   again, not as evidence for or against the  
9   health effect. And that's a study of male men  
10   from two states conducted by Shanna Swan and  
11   published in Environmental Health  
12   Perspectives.

13                  What Shanna Swan did was to take  
14   urine samples from this group of men who had  
15   evidence of abnormal semen characteristics,  
16   i.e., they were cases, and another sample of  
17   men who had normal semen characteristics, and  
18   assess their exposures to atrazine using a  
19   single urine sample measuring atrazine  
20   metabolites.

21                  So, again, it's another approach  
22   that I think adds to the breadth and depth of

1 our understanding of how epidemiology can  
2 contribute to the central question that will  
3 be discussed, as you pointed out, in  
4 September.

5           So, I think these other sorts of  
6 approaches have actually extreme relevance to  
7 the question about the use of epidemiology in  
8 risk assessment. And that's why, in  
9 particular, I understand your response. And  
10 I understand also that your task in September  
11 is very large, because this initial step of  
12 discussing various study designs and how these  
13 particular study designs can be incorporated  
14 into risk assessment, I think, is extremely  
15 important to the central question.

16           So, that's one point that I wanted  
17 to make, and I won't go through the examples  
18 that I selected, but they're well-known and  
19 they're published in the epidemiology  
20 literature.

21           The other point I want to make  
22 about incorporating these studies in the

1 weight of evidence approach, has to do with  
2 the potential shape of a dose-response curve.

3           That hasn't really been discussed  
4 here. So, we look at epidemiology studies,  
5 and many of us do the categorization of  
6 exposure using the quartile approach or using  
7 a tertile approach depending on the number of  
8 subjects that are in the study. And we, as  
9 has been described, let the exposure data, for  
10 example, in a case control study, let the  
11 exposure data for the controls drive the cut  
12 points for the analysis and apply those cut  
13 points to the cases.

14           So, that approach is obviously  
15 different from looking for a linear dose-  
16 response relationship that one might do with  
17 a regression analysis or other tools. And I'm  
18 not a biostatistician and others may wish to  
19 comment on this, but to me the issue is  
20 important because it goes back to the punitive  
21 mode-of-action of any chemical, that is, is  
22 there a linear dose-response relationship or

1 is there a threshold.

2 And we haven't really talked about  
3 thresholds and linear responses here and it's  
4 slightly outside the questions, but I believe  
5 it's relevant. Because if you were to take  
6 the epidemiology data, most of which is  
7 examined as Dr. Alavanja described, in terms  
8 of quartiles of exposure, you get one answer  
9 that might be referable to a mode-of-action  
10 that involves a threshold.

11 Whereas if you take the approach  
12 of using statistical tools that look for a  
13 linear dose-response relationship, you're  
14 looking at a different approach that answers  
15 a somewhat different question.

16 So, I just want to raise that  
17 because I think it's relevant to toxicologists  
18 and the people who do risk assessment, as  
19 another important consideration in beginning  
20 to understand what the epidemiology findings  
21 bring to the weight of evidence.

22 CHAIR HEERINGA: Thank you, Dr.

1 Reif.

2 Our next discussant is Dr. Lu.

3 Alex.

4 DR. LU: Since I'm assigned to  
5 address this charge question, so I can kind of  
6 aggregate my comments for various question to  
7 here, so I sort of hope to facilitate as  
8 proceeded here. It won't be long, anyway.

9 And also, I'm going to use some of  
10 the slide that presented in yesterday and  
11 today's public comment section, because I just  
12 realized that I learned a great deal from the  
13 previous presentation. I think they are  
14 useful in my address, in my response to these  
15 questions.

16 So overall, this is my opinion:  
17 That those ecological study that's cited by  
18 the agency may not suffer from so-called  
19 ecological fallacy to the level that EPA has  
20 acknowledged.

21 The evidence that presented in  
22 front of me, and including the data analyses

1 that present yesterday and today, actually  
2 suggests some possible link of atrazine  
3 exposure to birth defect.

4 For example, one of the slide I  
5 presented yesterday shows that if we were able  
6 to separate states from highest, medium and  
7 lowest atrazine use, we actually see a nice,  
8 seasonal effect. Meaning that during the  
9 early April, I'm talking about a highest  
10 atrazine state here, the increase of the birth  
11 defect is quite obvious and then that state  
12 assuming atrazine is the guilty party.

13 Take into account atrazine's half  
14 life in the water and the outcome of the birth  
15 defect measured monthly, they actually tell  
16 you something about the possible link.

17 How about those lowest atrazine  
18 state? Well, there is a signal trend, but not  
19 relevant to atrazine use. And keep in mind  
20 the atrazine is not the only teratogen or  
21 endocrine disrupting chemical that is being  
22 proposed right now.

1                   So, from here it's clear that  
2   there is a link. The question is that whether  
3   this is a true link or a false link, and this  
4   is where the ecological fallacy come into  
5   play.

6                   But it's obvious from this data  
7   analysis that we can rule out there's not  
8   generic variation associated with birth defect  
9   and associated with atrazine exposure.  
10   Otherwise, you will not see these type of a  
11   trend.

12                  So, again utilizing the data like  
13   this nature will kind of rule out some most  
14   likely not being part of the game plan.

15                  So, if we look at - now, say we  
16   have the national birth defect data which is  
17   not tied to individual state or individual  
18   regions. But what happen is that if we're  
19   able to link those incident data through data  
20   satellite in this case, atrazine concentration  
21   in the surface water versus number of tornado  
22   that hit in this area. I mean you start

1 thinking about maybe those are possible  
2 linkage, right?

3 And it's up to the agencies or  
4 people that are interested to prove whether a  
5 tornado is a likely cause or the atrazine.

6 So, again, based just on those  
7 data, I would like to address the question the  
8 agency posed in terms of so what should be  
9 incorporated in the overall weight of evidence  
10 analysis and the risk characterization for  
11 atrazine?

12 Well, I would look at, first of  
13 all, the window of susceptibility. The  
14 differences between this graph and the next  
15 graph is - well, the difference is obviously  
16 one shows some relationship, some show there's  
17 no correlation. But another difference is, is  
18 that this data analysis does not take into  
19 account window of accessibility.

20 One of the public comment  
21 presenter used the average or median  
22 concentration of atrazine in the water bi-



1 monthly, and then tabulate - and then  
2 correlate it with the small gestational age.

3           We know or based just on the paper  
4 that presented in front of the panel, we know  
5 that the time which is defined as last  
6 metrical period, is critical for birth defect.  
7 And if there is a significant amount of  
8 atrazine in the environment, this probably you  
9 will see.

10           So, I think window of  
11 susceptibility is very important in the weight  
12 of evidence analysis. Especially if the data  
13 has no such component, I think the agency  
14 should actually re-evaluate part of the data  
15 in a way that makes sure we do not introduce  
16 a virus.

17           The second important factor, I  
18 would say, is the longitudinal or temporal  
19 variation of exposures and the correspondence  
20 to the disease outcome. In this case, birth  
21 defect.

22           Again, we see clearly there is the

1 temporal variation. Now, the temporal  
2 variation of the atrazine correspond to the  
3 birth defect recorded. In this case it would  
4 be national level.

5 So, is this important? Maybe.

6 But if, say, for example, there is no atrazine  
7 variation month by month, whereas in the  
8 meantime you see a spike of birth defect  
9 reported in May, July, and you probably can  
10 rule out atrazine may not be an important  
11 player, or vice versa.

12 If the incidents of birth defect  
13 is distributed throughout the year, no matter  
14 how fluctuate atrazine concentration are in  
15 the drinking water or surface water, it  
16 doesn't matter. It's not an important player.

17 So, that's how I look at it in  
18 terms of you look at what should be  
19 incorporated into the weight of evidence  
20 analysis. I would put this two factors - I  
21 would weight these two factors heavily.

22 So, the next question is that

1 well, how are you going to address this  
2 epidemiology data?

3 Well, it's - again, my position  
4 here is that there's never a perfect epi study  
5 to address certain issues. So, we have to  
6 kind of think about what you have. And  
7 yesterday we spend some time to discuss this  
8 framework, and I found it very useful.

9 The reason because they tell you a  
10 lot about the evolution about biological  
11 plausibility in a sense.

12 For example, when we start using a  
13 lot of cell phones, we claimed that electronic  
14 magnetic field had something to do with brain  
15 tumors. There are animal data that strongly  
16 suggest that that's the case.

17 But as we go, there are some good  
18 human data - or epi data suggests that's not  
19 a case. So, we can move this box from here to  
20 here.

21 And yesterday we talked about  
22 melamine, which is the opposite case, right?

1 So, the question is that can we put the box of  
2 atrazine exposure and birth defect in one of  
3 the four boxes?

4 Obviously, it's not to the level  
5 we can put a box here, and neither here  
6 either.

7 So, the question is which one,  
8 where should we put it? You weight the  
9 evidence. Weight of evidence will help you.

10 The question to answer these two  
11 questions in terms of why did this pregnant  
12 woman living in - and I use this from the  
13 paper that we're assigned to read.

14 So, why does a pregnant woman  
15 living in Fort Wayne County, Indiana have a  
16 birth defect baby?

17 The answer to this question is not  
18 necessarily the same as the answer to this  
19 question. Why does pregnant women as a group  
20 living in Fort Wayne County, Indiana have so  
21 many birth defect babies?

22 So, the last factor I want to say

1 about the weight of evidence analysis  
2 approach, is that EPA needs to take into  
3 account the protection of public health. In  
4 my opinion, those ecological result actually -  
5 based on those ecological result, it is  
6 proven that agencies should leave these parts  
7 here.

8           There is some evidence for the  
9 associations, and leave for future datas. So-  
10 called good, quality epi data. Or in this  
11 melamine case, some incident data that dictate  
12 where this box that's temporally a part here,  
13 should go this direction or this direction.

14           Leaving the box here will actually  
15 safeguard public health with this part here.  
16 Will actually encourage more data because I do  
17 believe that one way or the other all the  
18 boxes here should be moved either to the  
19 Number 4 or Number 1 box.

20           So, that's just my comment. Thank  
21 you.

22           CHAIR HEERINGA: Thank you, Dr. Lu.

1 Dr. LeBlanc.

2 DR. LeBLANC: In gathering my  
3 thoughts to answer this particular charge  
4 question, I found a lot of repetitiveness in  
5 my thoughts. And I wanted to avoid that  
6 particularly as this day is coming to an end.

7 I was able to titrate my comments  
8 down to four points I'd like to make. And as  
9 I look at them now, I see there's still some  
10 repetitiveness in there, but I'll try and  
11 manage that as best I can.

12 Now, the first point that I have  
13 here is that the agency needs to give serious  
14 consideration to study selection, that  
15 difficult decision, perhaps, of what to use  
16 and what not to use.

17 In my experience, I could be in a  
18 room with a group of colleagues who are  
19 arguing that the EPA excludes relevant data in  
20 their risk assessment of a certain chemical.  
21 I could leave that room and go into an  
22 adjacent room, and hear another group of

1 colleagues talking about the same chemical and  
2 arguing that the EPA includes junk data in  
3 their risk assessment of that chemical.

4 And I suppose if you're making no  
5 one happy, maybe you're doing the right thing.  
6 But I think there is certainly a challenge  
7 there, and I think part of the answer at least  
8 is - well, there are two answers. Two parts  
9 to the answer.

10 One is making some good judgments  
11 as to how you go about selecting data, and  
12 then the other is being transparent in that  
13 decision making.

14 And I can only assume you thought  
15 a lot about this and maybe you've even had an  
16 SAP meeting about it, I'm not sure, but - I'm  
17 not suggesting another SAP meeting, by any  
18 means.

19 (Laughter.)

20 DR. LeBLANC: But I think there are  
21 considerations that go into that judgment and  
22 there can be quantitative approaches to data

1 selection. And you could take that approach,  
2 and you might be criticized by scientists  
3 saying that scientific judgment is involved.

4 And, again, I don't know the  
5 answer, and there are two sides to every coin.  
6 But there are - I think the EPA needs to give  
7 that a lot of thought.

8 I think it's an incredibly  
9 important point in making decisions as to how  
10 to use and incorporate this epidemiological  
11 data into the risk assessment of atrazine.

12 The second point is managing  
13 potentially new information. And this ties in  
14 with the points that I just made.

15 Say, for example, you have an  
16 epidemiological study where a novel  
17 observation is made with respect to potential  
18 effect, but that the decision had been made  
19 that the study wasn't going to be used.

20 If you simply file the study in  
21 the trash, I think you're setting yourself up  
22 for a lot of criticism that is they're not



1 using relevant data in their risk assessments.

2 But accordingly if you use it,  
3 then you're setting yourself up for they're  
4 using junk data in their risk assessment.

5 And I think that maybe what you  
6 need to do is when you find yourself in that  
7 kind of situation, that the information needs  
8 to be filed away not in the trash, and it's  
9 not used in the risk assessment at this point  
10 in time, but it's filed, it's put away pending  
11 further investigation so that everybody knows  
12 you're aware of the data and you haven't  
13 forgotten about it. And you just need some  
14 corroboration and you need greater information  
15 before you can actually use that information.

16 The third point I have is that  
17 consideration should be given to  
18 reproducibility of observations among studies.  
19 And certainly that is repetitive with a lot of  
20 things we've been talking about.

21 But the only point that I want to  
22 make here is that we need to be thinking about

1 reproducibility or consistency not only in  
2 effects that are observed in epidemiological  
3 studies, but where possible the concentrations  
4 at which those effects occur.

5           In the ecological world, I don't  
6 hear a lot of controversy with respect to the  
7 effects that atrazine causes among exposed  
8 amphibian populations. The controversy that  
9 I hear relates to the concentrations of  
10 atrazine at which these effects occur.

11           And I don't think you can separate  
12 the two. I don't think it's fair to say  
13 atrazine does this. The question is does  
14 atrazine do that at an environmentally-  
15 relevant exposure concentration?

16           And the last point I have is that  
17 the agency needs to continuously pose the  
18 question. The question being to what degree do  
19 the epidemiological studies decrease  
20 uncertainty with extrapolation from animal  
21 studies to the protection of human health?

22           Certainly in my mind, that's the

1 big question. We've discussed a lot of  
2 points, a lot of items in the past could of  
3 days, but I think it all titrates down to  
4 whether or not the epidemiological studies  
5 allow us to reduce the uncertainty associated  
6 with extrapolations.

7 And whatever the answer to that  
8 question is, the agency needs to use that  
9 answer in adjusting uncertainties accordingly  
10 in determining what uncertainty factors might  
11 be applied to the risk assessment of atrazine  
12 or other chemicals.

13 CHAIR HEERINGA: Thank you, Dr.  
14 LeBlanc.

15 Dr. Bove.

16 DR. BOVE: Well, I think we've been  
17 over and over all these issues, but let em  
18 just say a few things.

19 One, I do think that study  
20 selection is important, and I would want EPA  
21 to error on the side of being totally  
22 comprehensive as they can, including going

1 through the gray literature if necessary.

2 Cast the net widely, and then give  
3 reasons why you're going to exclude studies.  
4 Good reasons.

5 But that gets me to another point.  
6 And that is that I think that when EPA is  
7 evaluating the epi research, they need to have  
8 epidemiologists review it. If they need to  
9 get help from outside, get help from outside.

10 So, if you're looking at drinking  
11 water studies, have expertise not only in -  
12 not only bring people in who have done these  
13 kind of studies, but also people who have done  
14 drinking water exposure assessment, done water  
15 distribution system modeling, groundwater fate  
16 and transport modeling, whatever. So, you have  
17 the right expertise evaluating these studies.

18 Similarly for occupational  
19 studies. Bring in the epidemiologists who  
20 have done these studies. Bring in the IH  
21 people who have done the exposure assessments,  
22 and have the right expertise there to evaluate

1 these studies as you probably do with the tox  
2 studies.

3 So, I don't think I'm asking for  
4 something a whole lot different. Just  
5 bringing in the right expertise for these  
6 studies, I think that would help.

7 And, again, I think that when I  
8 hear that we want to see if the human data  
9 help in the extrapolation from animal data,  
10 again I want to get away from thinking that  
11 there's one set of data that's much better  
12 than another set of data.

13 Again, the epi data is looking at  
14 the right species, it's looking at the right  
15 exposures, it's looking at the right ways that  
16 people get exposed. So, granted there are  
17 advantages to tox studies and animal studies,  
18 I'm not going to dispute that, but there are  
19 also advantages of epi studies.

20 And I think the better idea is to  
21 look at both sets of data and see what it  
22 tells us and not assume that we'll get the end

1 point from one and see if the other data set  
2 agrees with it or not. Look for the most  
3 sensitive end point that is being told to you  
4 by both data sets, and move forward in that  
5 way.

6 CHAIR HEERINGA: Thank you, Dr.  
7 Bove.

8 Comments from other members of the  
9 panel in response to this? Dr. Portier.

10 DR. PORTIER: I just had a  
11 clarification question, Dr. Bove. When you  
12 said bring in these outside experts, are you  
13 brining in the people who did the studies of  
14 the concern or are you brining in people who  
15 have done those kind of studies, but not the  
16 ones being, you know, is it the owners of the  
17 studies or people who know how to do those  
18 studies, but who could be freer to be critical  
19 of the studies?

20 DR. BOVE: The EPA could make that  
21 decision. Certainly you'd want people there  
22 who know how to do these studies, who know the

1     pitfalls, who know how difficult it is and  
2     what these studies can actually tell you.

3                 So, if the only people around are  
4     the people who actually did those studies, I  
5     guess you're going to have to include them.  
6     But I'm sure there are people out there,  
7     epidemiologists out there who have done  
8     drinking water studies on other end points.

9                 For example, I've never done a  
10    drinking water study on atrazine. I've done  
11    drinking water studies on TC, PC and so on,  
12    for example.

13                There are water modelers who maybe  
14    haven't done groundwater fate and transport of  
15    accuracy, but have done floor solvents or  
16    gasoline or whatever.

17                So, there is that expertise out  
18    there. Okay. So, I think you can find it.  
19    I think you can find it.

20                CHAIR HEERINGA: Dr. Chambers.

21                DR. CHAMBERS: I'm getting a little  
22    uncomfortable with a few of the answers that

1 have come up with this afternoon, this  
2 question, and earlier on some conclusions  
3 about atrazine.

4 I think the point of all of your  
5 questions at this point in time is generic  
6 methodological types of questions. And that  
7 this is - it's premature at this point, I  
8 think from your standpoint, and from our  
9 standpoint, to make any conclusions about  
10 atrazine's effects as such.

11 I'll be very uncomfortable if our  
12 report starts making some judgments at this  
13 point, because I think that's the point of the  
14 September meeting. And I would urge the panel  
15 to refrain from putting some conclusions about  
16 atrazine's effect at this point, because the  
17 data sets that you're providing us are not  
18 complete at this point.

19 CHAIR HEERINGA: Thank you, Dr.  
20 Chambers.

21 Dr. Lowit.

22 DR. LOWIT: Just to respond to Dr.



1 Chambers and not to cut off a lot of  
2 productive discussion, but I think there's  
3 certainly elements of what we thought we would  
4 hear in 2.4, we actually heard in 2.3, the  
5 cautions about individual studies and the way  
6 to think about those individual studies in a  
7 way that maybe we haven't yet in both the  
8 generic and the specifics of it.

9 I'm not encouraging you to cutting  
10 it off. I just -

11 CHAIR HEERINGA: No, I understand  
12 what you're saying with respect to the  
13 discussion in 2.3 has in fact identified a lot  
14 of the character of the individual studies  
15 that would be relevant to bring forward to  
16 this assessment.

17 Dr. Portier had a comment.

18 DR. PORTIER: This is just coming  
19 from my experience. When you bring in experts  
20 to review these things, the first thing you  
21 have to do is get them to all agree on what  
22 are the criteria of what they, as a group, are

1 going to call a good and a bad study for that  
2 objective.

3 I've done these things where you  
4 get in and you immediately start reading the  
5 studies and you're trying to develop these  
6 criteria as you go along, and it changes.  
7 After you've read a whole bunch of bad  
8 studies, a kind of good study looks really  
9 good, right? And it's better if you can - and  
10 it's even better if EPA kind of lays down some  
11 general ground rules before you even bring  
12 them into that evaluation.

13 So, I totally agree that's the way  
14 to go for a lot of this stuff in terms of  
15 especially looking at utility and trying to  
16 put weights on utility. You're not going to  
17 get that statistically, but you're going to  
18 get that from a consensus assessment of the  
19 expert.

20 So, there's got to be a box around  
21 that. Otherwise, it becomes a moving target.

22 CHAIR HEERINGA: Thank you, Dr.

1 Portier.

2 I think what I would like to do at  
3 this point is to move on to Charge Question 3.  
4 And just looking ahead for this afternoon, it  
5 would be my intent to try to wrap up Charge  
6 Question 3 per our agenda this afternoon. And  
7 we will try to take care of Charge Question 4  
8 tomorrow morning.

9 And I think that we should  
10 probably be fairly close to the agenda.  
11 Whether we finish - I don't want to force it  
12 to finish before noon. But I think if we have  
13 three-and-a-half hours tomorrow morning on  
14 Charge Question 4 and wrap up, we should be  
15 pretty close to finish just to sort of give  
16 you a forward look at this.

17 But if we could read Charge  
18 Question Number 3.1 into the record?

19 DR. LOWIT: We're going to do some  
20 quick musical chairs if you give us a second.

21 CHAIR HEERINGA: Sure.

22 CHAIR HEERINGA: Sarah Winfield.

MS. WINFIELD: Case study C

describes various analyses and evaluations that can be conducted when evaluating human incident data. Please comment on ability to use incident data for the following types of analyses: trend of incidents over time, frequency of reported symptoms, common product clusters, frequency of repeated exposure scenarios, and assessment of children versus adult symptom profiles, which is in the diazinon case study, and please suggest alternative and/or additional analyses, if appropriate.

CHAIR HEERINGA: Our lead

discussant is Dr. Lu.

DR. LU: I guess I'm going to start

by saying that the human incident data for diazinon is quite unique in the way that those are acute toxicity regardless of how the data were gathered by different agencies.

And also the dose acute toxicity

or the report of symptoms are very unique to

1 all the member in the OP families.

2           So, I mean it's unlikely that we  
3 discuss in this case of diazinon would be  
4 attributable to other pesticide group such as  
5 triazine herbicide which does not have  
6 significant acute toxicity or very apparent  
7 symptoms that people can report it to.

8           So, I mean this alone would pose a  
9 significant limitation for future utilizations  
10 in this weight of evidence analysis and risk  
11 characterization.

12           The other limitation which the  
13 agency has acknowledged is that those incident  
14 report data are in terms of the quality, those  
15 incident report data are varies to a great  
16 extent. And the trouble is we don't even know  
17 how to quantify those variations. We don't  
18 know which one is good, which one is bad, and  
19 so on and so forth.

20           So, there's no doubt that if we  
21 are going to - if the agency is going to  
22 incorporate those acute incident symptoms or

1 data, it will introduce unwanted bias and  
2 likely uncertainty to the future analysis.  
3 So, just in my opinion, those are my  
4 disclaimers.

5 Speaking of trend of incident over  
6 time, diazinon data obviously shows that once  
7 the use of certain pesticides is limited, the  
8 reported symptoms in terms of the number and  
9 the frequency were reduced as well. And I  
10 think that's the intention of restricting  
11 diazinon and other opiate pesticide use.

12 However, it's not clear that at  
13 the population level the exposure to diazinon,  
14 that will not trigger acute symptoms also  
15 reduced.

16 So, I'm talking about the emphasis  
17 on acute toxicity versus chronic health  
18 effect. Although we see a great reduction of  
19 self-report symptom data throughout this  
20 country, but there are exposure that has  
21 actually triggered no effect, no apparent  
22 poison symptoms at all. So, how would you

1 account for those chronics?

2 This is even worse for pesticides  
3 that does not have apparent or dramatic acute  
4 toxicities like triazine herbicide, for  
5 example. So, I will suspect that the incident  
6 report for those pesticides will be sparse,  
7 inconclusive.

8 In other words, are their report,  
9 the incident report related to atrazine,  
10 related to one of the pyrethroids and so on  
11 and so forth.

12 So, having said that, there is  
13 important value for the incident data over  
14 time for use in risk characterization and risk  
15 assessment. So, the apparent decline of  
16 diazinon OP is related to a restriction of  
17 use, right?

18 So, what I just mentioned in  
19 Question 2.4 is that if - this is  
20 hypothetical. If we were able to remove  
21 certain pesticides, in this case the topic of  
22 discussion, atrazine, if we were able to

1     remove atrazine from the water bottle in the  
2     critical month of women get into pregnancies,  
3     will we see a reduction in birth defects  
4     nationwide?

5                 That's the value of looking at a  
6     trend of incident over time by taking away a  
7     pesticide or compound and we know was related  
8     to the health effect, and see whether that  
9     health effect will disappear as well. And  
10    that will actually enhance the hypotheses of  
11    certain chemical cause certain health effect.

12                And that could be done, but it  
13    would take a while. And that's what I'm  
14    suggesting.

15                If you think about a two-by-two  
16    box, it's prudent to put something in evidence  
17    against or evidence for and waiting for the  
18    new data to move the boxes around.

19                And data like incident trend over  
20    time manipulate by restriction of pesticide  
21    use or complete removal from the market, will  
22    help you to see whether this is the case.



1                   And this is the second question in  
2 terms of frequency report symptoms. I'm going  
3 to lump this with the frequency of report  
4 exposure scenario, because I do think they are  
5 - you are asking the same questions.

6                   In report symptoms, especially the  
7 similar symptoms or exposure by different  
8 individual within a defined time period might  
9 raise some concern not only for the use of  
10 patterns of that specific product, but also  
11 the potency of acute toxicities that has not  
12 yet been discovered or disclosed.

13                  In the circumstances in which  
14 incident data reveal a health outcome that is  
15 not previously observed in the toxicological  
16 studies, right, those human incident data will  
17 be quite valuable in terms of exploring  
18 unfounded biological plausibilities associated  
19 with the specific exposures.

20                  So, move on to the next question  
21 is common product clusters. We spent some  
22 time talking about clusters. There are

1 confusing points, there are some  
2 misclassification, but cluster also provides  
3 some valuable information.

4 For example, the cluster actually  
5 occurred, right? But it's more of an acute  
6 public health concern instead of a risk  
7 assessment purpose.

8 For example, many years ago there  
9 is an incident on methyl pyrrithione in ten or  
10 13 states in the southeast regions. And we  
11 finally found out through ATSDR, it was caused  
12 by misapplication.

13 So, again, those information are  
14 critical for acute public health mitigations,  
15 but what is the value of the risk assessment?

16 It's an application error. It's  
17 almost a misapplication. It's supposed to not  
18 happen.

19 So, gain, I actually raise the  
20 question about cluster data. And sometimes  
21 it's manipulated, it can happen because of  
22 misapplication, it's totally irrelevant to

1 regulatory risk assessment.

2 And the last question is  
3 assessment of children versus adult symptom  
4 profiles. This is my knowledge that the known  
5 acute toxicity of OP or diazinon is not  
6 differential between adults and the kids.

7 The dose that will trigger the  
8 acute toxicity might be different between the  
9 adult and the kids, but self-report incident  
10 data really contain exposure dose information.

11 So, again, I don't see how you can  
12 use those for assessing children versus adult  
13 exposure.

14 So, in conclusions, I will say  
15 incident data like diazinon has some value for  
16 risk characterization, especially for  
17 pesticide other than OP. But its value for  
18 risk assessment, in my opinion, is highly  
19 limited.

20 I'll stop here.

21 CHAIR HEERINGA: Thank you, Dr. Lu.

22 Dr. Chambers. Jan.

1 DR. CHAMBERS: I'm not really  
2 familiar with incident data. So, seeing this  
3 was my first pass at looking at that kind of  
4 compilation and I found a fair amount of it  
5 pretty confusing.

6 With respect to trends of  
7 incidents over time, I think this is, as Alex  
8 pointed out, this is a very good example since  
9 the numbers of incidents decreased with the  
10 decrease of approved uses of diazinon.

11 I think you have a pretty unique  
12 case here that will probably not be duplicated  
13 with other pesticides. And so how  
14 generalizable this is for the use of incident  
15 data is kind of hard to say. Probably not  
16 very generalizable.

17 With respect to frequency of  
18 reported symptoms, these can be tallied, but  
19 the tallies do not discriminate, as near as I  
20 can tell, between high and low exposure in  
21 Table B1.

22 Also, with the low numbers of

1 incidents such as the PISP had two incidents,  
2 the percent response don't make any sense when  
3 you have very, very low numbers. So, I don't  
4 know how you interpret that meaningfully.

5 Table B5 shows absolute numbers,  
6 but wasn't clear to me whether the symptoms in  
7 the generic categories are the same. And so  
8 if they're blending a lot of different  
9 symptoms into this generic category, then that  
10 may not tell you a whole lot either.

11 Another thing you asked about was  
12 common product clusters. And I guess I saw  
13 that in Table B, too, but I wasn't sure of  
14 what that actually was telling us. So, I  
15 don't know how to interpret that either.

16 Frequency of repeated exposure  
17 scenarios, I couldn't find where that was  
18 compiled. So, maybe that was in there and I  
19 just missed it, but I couldn't find it.

20 Assessment of children versus  
21 adult symptom profiles. These are compiled,  
22 but again it's unclear for similar symptoms

1 between children and adults at least with this  
2 presentation.

3 So, maybe there's a lot of  
4 information out there that really got compiled  
5 very, very briefly here, but I couldn't  
6 discriminate a lot of the stuff that was there  
7 that maybe is useful.

8 You asked for potential  
9 alternative and additional analysis. About  
10 the only thing I can think of that might be  
11 worthwhile is to separate out the suicides and  
12 abuses of intentional exposures as opposed to  
13 just accidental exposures.

14 The accidental exposures will tell  
15 you a little bit more - or will tell you  
16 something about potential risk management  
17 issues or if the intentional exposures are  
18 just totally random. So, they would not tell  
19 you much about how your risk management  
20 processes are going ahead.

21 Any confounders or other factors  
22 that were present that may have been

1 responsible in whole or in part for the  
2 symptoms reported should be determined. And  
3 if significant, then the reliability of that  
4 incident report should be questioned.

5 But then kind of back to the  
6 earlier question this morning, is it worth the  
7 time and energy of your staff to really dig  
8 into these data when they're going to be sort  
9 of isolated bits of data and maybe not really  
10 contribute to the quantitative risk assessment  
11 in any meaningful way.

12 CHAIR HEERINGA: Thank you, Jan.

13 Dr. Gold.

14 DR. GOLD: I took this question  
15 sort of generically. I figured the case study  
16 was just kind of an example and that you  
17 wanted more generic input on use of incident  
18 data. So, that's how I answered it, and I  
19 have a few points.

20 I think the advantage of these  
21 sources for evaluating incidents, trends and  
22 so forth, is that the data are collected in a

1 relatively uniform manner with regard to  
2 product information or severity rankings and  
3 symptoms. So, that enhances the comparability  
4 of the data sort of over time.

5 The disadvantage is, I think,  
6 though, in using these kinds of data for the  
7 kinds of scenarios that you've outlined, are  
8 several. One is the lack of mandatory  
9 reporting by anyone other than registrants, so  
10 that you are likely to have under-reporting.

11 Second, the potential lack of  
12 concomitant information on trends in the  
13 amount of pesticide use so that it's not  
14 possible to determine if there are really more  
15 incidents or more usage.

16 And third, that you're largely  
17 only capturing - and this was stated  
18 previously - only capturing an acute event and  
19 not events that have long latent periods or  
20 are associated with long-term exposures.

21 So, I think the human incident  
22 data may be useful in the problem formulation



1 stage in suggesting future research that  
2 should be performed and data that should be  
3 analyzed to assess better the magnitude of the  
4 relationship of specific types, doses and  
5 amount of exposure to specific health  
6 outcomes.

7 Also, providing evidence for  
8 mitigation efforts and providing information  
9 on whether human effects are consistent with  
10 those observed in toxicologic studies of  
11 animals.

12 In terms of the comparison of the  
13 distribution of symptoms in children and  
14 adults, I think it can provide supportive  
15 evidence. But I think the lack of similarity  
16 does not necessarily mean that the mechanisms  
17 are different, because they could also reflect  
18 different levels of sensitivity report. For  
19 example, people might be more likely to report  
20 symptoms in children than in adults. Just  
21 higher sensitivity.

22 Also, different routes of exposure

1 might occur in children versus adults. Kids  
2 put everything in their mouth. Adults are a  
3 little more selective.

4 And different sizes of the  
5 population exposed so that if you really have  
6 small numbers that are exposed, this could be  
7 resultant in less certainty in the  
8 distribution of symptoms.

9 CHAIR HEERINGA: Thank you, Dr.  
10 Gold.

11 Dr. Pope. Carey.

12 DR. POPE: Well, just similar to  
13 Dr. Chambers, I haven't really looked at this  
14 kind of information much in the past. I  
15 thought that it appeared to be that all these  
16 reporting systems were pretty effective at  
17 detecting changes over time that made sense  
18 with the changes in use of this particular  
19 one.

20 And, therefore, use of this  
21 information looks pretty good for looking at  
22 effects of risk mitigation and management

1 processes.

2 In general the reporting systems,  
3 I thought, picked up relatively similar  
4 frequency, some signs and symptoms. There  
5 were some differences in categories like  
6 miscellaneous signs that may fit in with other  
7 categories from other reporting systems.

8 So, there were differences in  
9 terminology. And, also, it was noted that  
10 severity of signs or the symptoms could be  
11 different between these different reporting  
12 mechanisms.

13 So, it seems like maybe some more  
14 useful information could be gathered if you  
15 make more common recording instruments, if  
16 that's possible, between these different  
17 procedures and systems.

18 I think with regard to knowledge  
19 of repeated exposures, it seems this was not  
20 going to be nearly as relevant as incident  
21 reports for single exposure incidents.

22 Regarding the subpopulations with

1 the caveats that Dr. Gold just said, I think  
2 there is potential to gain something out of  
3 differential subpopulations and their  
4 responses from this kind of data.

5           The limitations regarding the  
6 knowledge of specifics of exposure, I think,  
7 is for me the biggest problem with this data  
8 as far as what a person or particular  
9 incident, what kind of exposure the person  
10 had.

11           It would seem to me that this may  
12 not even be for a - in this case, it may not  
13 be a diazinon exposure with certainty. So, I  
14 think that's a serious weakness.

15           I think a good strength of this  
16 kind of information is unanticipated  
17 responses. And I think someone mentioned  
18 earlier the idea of vigilance. I think this  
19 fits very well in here.

20           Vigilance for this kind of  
21 information resource can pick up unanticipated  
22 responses that might suggest you look at

1 alternative mechanisms of toxicity that  
2 haven't come - haven't shown up in the risk  
3 assessment processes before.

4                   So, for me the bottom line is that  
5 I think any information on pesticides can be  
6 used in the risk assessment process, but I  
7 think, for instance, data probably have  
8 relatively minimal influence on the  
9 quantitative aspects of the risk assessment  
10 process.

11                   CHAIR HEERINGA: Thank you, Dr.  
12 Pope.

13                   Dr. LeBlanc.

14                   DR. LeBLANC: I don't have much to  
15 add here. I certainly concur with my  
16 colleagues with respect to trends of incidents  
17 over time that this is a good measure of  
18 success in the risk management process.

19                   And I think diazinon sort of  
20 represents a gold standard exemplifying the  
21 utility of evaluating trends and incidents.  
22 And it may very well be that a few other

1 chemicals will meet that standard, but  
2 nonetheless I think it's an important measure.  
3 One that should be used in the analysis of  
4 incident.

5 Frequency of reported symptoms, I  
6 think that this is important and can be used  
7 to help establish plausibility.

8 For example, we've talked a lot  
9 about biological plausibility in our  
10 discussions at this meeting. But independent  
11 of biological plausibility if a hundred  
12 farmers report an implausibility toxicity  
13 following exposure to a pesticide, I think the  
14 agency needs to take notice of that and act  
15 accordingly.

16 Assessment of children versus  
17 adult symptom profiles I think is warranted.  
18 I think we all recognize the possibility, the  
19 potential for susceptibility differences.  
20 Certainly differences in exposure patterns  
21 that may exist between children and adults.

22 And just something I wonder, and

1 that is whether there are similar incident  
2 databases for non-human populations such as  
3 pets. And if there are, whether they are  
4 considered in looking at incidents, because it  
5 seems to me that pet incidents might serve as  
6 a good surrogate to exposure as it relates to  
7 children.

8 CHAIR HEERINGA: Thank you, Dr.  
9 LeBlanc.

10 Dr. Manibusan.

11 DR. MANIBUSAN: Sure. I just want  
12 to respond to the question of whether the  
13 agency considers other incident data beyond  
14 human data.

15 We do consider pet incident data  
16 as well as ecological incident information.  
17 And rather timely that you asked this question  
18 since we've just completed a really  
19 comprehensive review of the spot-on pet  
20 incident data for fleas and ticks, controls of  
21 fleas and ticks.

22 And we actually look to using

1 these same kind of opportunities to scrutinize  
2 this information in terms of from a  
3 surveillance standpoint, as well as  
4 understanding consistency, reproducibility,  
5 understanding where there's opportunities  
6 where we can do a better job in labeling,  
7 because we're seeing a lot of misuse of the  
8 product. For example, there might be a lot of  
9 situations where dog products are used on  
10 cats.

11               Where can we do a better job in  
12 risk reduction is very important for the  
13 agency.

14               I think, Dr. Chambers, you brought  
15 up a very good point. This information is  
16 very, very useful to look at trends and  
17 patterns and clusters in that way. And in  
18 particular, looking at product level  
19 clustering.

20               Because that gives us a sense  
21 going back, at trying to target whether it's  
22 the active ingredient or the inert or the



1 combination that really is causing the effects  
2 reported.

3 CHAIR HEERINGA: Dr. Levine.

4 DR. LEVINE: Tina Levine. I just  
5 want to point out in a way it's kind of a  
6 separate kind of analysis.

7 One thing, the kind of data that  
8 we get on pets is aggregated. We don't get  
9 the individual case reports that we get for  
10 humans. They just send aggregate data.

11 And, also, we're not - we  
12 generally don't look at pet incidents in  
13 trying to evaluate what might be happening in  
14 humans. We're looking at the pet incidents in  
15 terms of what's happening in the pets.

16 CHAIR HEERINGA: Dr. Reed.

17 DR. REED: I think what I wanted to  
18 say is probably all said early on already with  
19 the Question 1.2. And I think what I heard is  
20 pretty much what I have in mind. But since my  
21 list is very short, I'll just repeat that.

22 But a philosophical difference, I

1 think, with being a risk assessor and looking  
2 at data is that when we talk about this  
3 particular type of data seldom has sufficient  
4 exposure data, I, in my brain, I translate it  
5 in terms of so it's not none, it's just  
6 seldom.

7           And so if we say that it has  
8 limited usefulness, in my mind I'm saying  
9 okay, so indeed we didn't say that it was  
10 never useful.

11           So, in risk assessment, we do take  
12 into account all the data that we have. Sort  
13 of how we do it at least within our group, is  
14 that we will still look at all the data that  
15 we have, including incidents data, and you can  
16 quickly scan through what might be useful,  
17 what might not be, and then go from there.

18           And as I said, there's two ways of  
19 looking at these types of data. One is  
20 looking at holistically as a group, and the  
21 other way is to pick out which ones might be  
22 useful.

1                   And I think early on we mentioned  
2 something about the aldicarb in watermelon.  
3 And if that is considered as incidents data,  
4 it turned out to be it was very useful. We  
5 even came up with dose-response out of what's  
6 in people's refrigerator when the next day you  
7 go and collect these there.

8                   So, I would not want to discourage  
9 the agency by saying it's not very useful, but  
10 I think it's important to look at these type  
11 of data with all the caveats that we have  
12 mentioned today, but not to dismiss it.

13                  CHAIR HEERINGA: Thank you, Dr.  
14 Reed.

15                  I think, Sarah, we're willing to  
16 go on to Question 3.2.

17                  MS. WINFIELD: OPP plans to conduct  
18 analyses of human incident data like those  
19 described in Case study C for other pesticides  
20 undergoing registration review. In light of  
21 the scientific issues discussed in Question  
22 4.1, OPP requests input from the panel on

1 factors to consider when evaluating the  
2 reliability of human incident data and  
3 determining the relative weight that should be  
4 placed on such data in risk assessment/risk  
5 characterization or in problem formulation.

6 CHAIR HEERINGA: Our lead  
7 discussant is Dr. Chambers.

8 DR. CHAMBERS: Thank you. In my  
9 opinion, very little light should be placed on  
10 incident data for all the reasons that have  
11 been discussed in the last couple of  
12 questions.

13 Now, notwithstanding Ruby's  
14 comments a few minutes ago that can identify  
15 certainly something like aldicarb in  
16 watermelons that was unanticipated, and you  
17 should be alert to situations like that where  
18 you've got a cluster of something that is  
19 unanticipated.

20 But my sense of most of this  
21 incident data is that they have a very diverse  
22 nature with regard to estimated dose levels,

1 product characteristics, the ability of the  
2 observer to accurately assess symptoms, and  
3 just kind of a scatter of information.

4           So, for the most part I don't  
5 think they're going to be very, very useful in  
6 any kind of quantitative risk assessment since  
7 the numbers of incident reports are great,  
8 such as what Ruby pointed out for Temik in  
9 watermelons.

10           If the exposures are well  
11 estimated and the symptoms are highly  
12 consistent, then perhaps the incident data  
13 would be useful, and you've done this in that  
14 particular case.

15           In cases of abuse or suicide, the  
16 data would not be very helpful for overall  
17 risk management because these exposure levels  
18 would be well beyond label recommendations and  
19 wouldn't be accidental exposures.

20           If reports are mainly described  
21 like flu-like symptoms or symptoms that could  
22 arise from physiological stress from the fear

1 of poisoning or something like that, then I  
2 think that could be general symptoms for a  
3 variety of illnesses or conditions and it may  
4 be impossible to distinguish the pesticide  
5 effects from other confounding conditions such  
6 as infectious diseases or just general stress.

7 Certainly fear of poisoning could  
8 lead to symptoms that are just sympathetic  
9 nervous system reactions. And so I think you  
10 need to be alert to that.

11 The incidents are mostly going to  
12 be short-term type things. In many cases  
13 you're interested in long-term effects. And  
14 they won't give you much information along  
15 those lines.

16 The diazinon situation is probably  
17 uniquely suited for such an analysis. We've  
18 mentioned that before because of the types of  
19 clear symptoms that can be experienced acutely  
20 from an anti-cholinesterase and because of the  
21 risk mitigation measures of removing diazinon  
22 from residential uses and the consequent

1 reduction in incidents.

2 Most other pesticides that you're  
3 probably going to try this for would not  
4 probably be, in my opinion, as adaptable to  
5 such a clear presentation.

6 And I'm not saying don't do it,  
7 but I don't think you're going to get  
8 something that's as clear-cut as this since  
9 it's an organophosphate and you have the same  
10 sort of risk mitigation type thing.

11 CHAIR HEERINGA: Thank you, Dr.  
12 Chambers.

13 Dr. Lu.

14 DR. LU: One remedy for overcome  
15 the severe limitation of using incident data  
16 like reported as for diazinon, is that maybe  
17 the EPA should work out with some kind of  
18 agreement with the agency that collect those  
19 data.

20 So, in the future when the case is  
21 calling and reported symptoms and ask them to  
22 donate some specimen sample so in a way that

1 you can determine the reliability of the case  
2 that it's just reported.

3 Say, for example, there's an OP  
4 poisoning case. And in this case it will be  
5 accidental. I agree that the suicide and so  
6 on and so forth, those data should be tossed  
7 away because it's not true data.

8 But if the agency were able to  
9 work out some agreement in terms of getting  
10 specimen sample from the cases as reported,  
11 not only you can test the reliability of the  
12 case as just reported, you can also see what  
13 is the level actually will trigger the  
14 symptoms that's reported and so on and so  
15 forth.

16 It can be labor intensive. And I  
17 understand that different agency has different  
18 mandate in terms of why they collect those  
19 data. And getting a specimen sample may not  
20 be their highest priority, but I think it's  
21 really needed, essential.

22 Especially nowadays CDC has the



1 mechanism that once you submit a sample, they  
2 can analyze and turn around rather quickly.  
3 So, it's not the problem. The problem is  
4 whether those agency will be cooperative in  
5 the matter.

6 But without a specimen sample,  
7 that's preferable. If not, a surrogate sample  
8 will be okay. But without those hard  
9 evidence, you never know whether that's a true  
10 positive or false positive cases.

11 I just don't know how you can  
12 screen those data without solid evidence in  
13 terms of the level that you can measure in  
14 that person.

15 CHAIR HEERINGA: Thank you, Dr. Lu.  
16 Dr. Pope.

17 DR. POPE: Yes, I basically agree  
18 with the comments preceding. I just hit a  
19 couple of - one point, actually. Someone  
20 mentioned earlier about the longer term  
21 effects.

22 And I know with OPs after acute

1     intoxication, you have the long-term effects  
2     that some - I'm not suggesting that it be  
3     incorporated in these incident reporting  
4     mechanisms, but all of these people gain some  
5     information whether they do have some kind of  
6     long-term effect would be useful.

7                     And then just reiterate once again  
8     I think that this kind of information is  
9     useful, but probably in a qualitative sense  
10    for risk assessment.

11                    CHAIR HEERINGA: Dr. Bailar.

12                    DR. BAILAR: I agree with OPP that  
13    despite their limitations, incident data sets  
14    are an important resource of Hill surveillance  
15    information on registered pesticides.

16                    Weak as they are, they're  
17    sometimes the only data available. And  
18    sometimes weak is good enough for OPP's  
19    purposes.

20                    OPP uses five different sources of  
21    incident data. I assure you there is some  
22    overlap in reported cases, but how much

1 overlap is concentrated on more severe  
2 poisoning or in certain geographic areas or in  
3 other ways.

4 It seems that these sources are  
5 studied independently until the last stages of  
6 analysis when results are put side-by-side to  
7 look for signals of a problem.

8 There seems to be a need to a  
9 research study to consider how these five  
10 sources might be used in combination at  
11 earlier stages not necessarily by matching  
12 cases, but at least by organizing the data in  
13 ways that draw on the various strengths of the  
14 sources. This might be accomplished by a  
15 focused study in one or two areas where three,  
16 four or all five reporting systems operate.

17 Similarly, there is a need for  
18 study of clustering of reported cases. It is  
19 not clear how multiple human problems in two  
20 or more persons exposed together are handled.

21 In my view, a cluster is likely to  
22 indicate a more severe problem than an

1 isolated case, but not more severe in  
2 proportion to the number of persons reported.

3 This is because reporting of one  
4 is likely to stimulate reporting of others in  
5 the cluster so that the cluster is  
6 artificially inflated over what would happen  
7 if reporting of individuals were independent  
8 and it's not clear how the data sets handle  
9 multiple reports about effects on the same  
10 person at different times.

11 It's well-recognized in he study  
12 of accidents, generally, that some persons are  
13 accident prone, but others are report prone.  
14 That is, they're unusually likely to perceive  
15 and report a problem. Even a very minor or  
16 non-existent one. This also needs study.

17 It seems to me that OPP should  
18 consider somewhat different approaches for  
19 chemicals that are transient in the human  
20 body, for example, some light aromatics, and  
21 those that are cumulative, for example, heavy  
22 metals or fat-soluble chemicals.

1                   Data needs might differ with  
2   respect to exposure parameters, history of  
3   prior adverse reactions and other things.

4                   Of more direct importance to OPP,  
5   modes of analysis and the concerns about  
6   interpretation may differ. I'm not sure that  
7   these can be comfortably accommodated in a  
8   single analysis.

9                   To illustrate though I'm not sure  
10   how much of this will be available, some items  
11   especially critical to the study of acute  
12   toxicants, are severity in relation to recent  
13   exposure, immediacy of response after exposure  
14   and short-term group effects.

15                  Some items that are especially  
16   critical to study, accumulative toxicants,  
17   severity is less important, the course of  
18   development of symptoms is important, and  
19   short-term group effects can argue against  
20   toxicity of the chemicals.

21                  Some items that are critical study  
22   in both are consistency with animal data and

1 with findings for related chemicals, evidence  
2 of misuse and clustering effects in persons  
3 tending to be exposed together.

4 There's a figure here, Figure C1,  
5 that shows a high frequency of miscellaneous.  
6 This should be broken out if that is feasible.

7 Also I'm concerned that here as I  
8 was for atrazine, that chemical toxicants  
9 simply do not generally have a very broad  
10 range of human health effects. Some do, but  
11 most do not, and this can be a red flag of  
12 pervasive bias.

13 Overall, it appears to me that  
14 this document is meant to give quite general,  
15 even somewhat vague advice, and to encourage  
16 and rely on the good judgment of informed  
17 scientists to draw appropriate conclusions  
18 which will necessarily be weak in the best of  
19 circumstances. I concur.

20 CHAIR HEERINGA: Thank you, Dr.  
21 Bailar.

22 Comments from other members of the

1 panel. Dr. Reif.

2 DR. REIF: Just briefly two  
3 thoughts about incident data and their  
4 potential usefulness.

5 First, validated instances of  
6 incidents regarding acute pesticide or other  
7 chemical poisonings or toxicities create the  
8 opportunity for either longitudinal follow-up  
9 studies or historical cohort studies to  
10 evaluate long-term effects of single exposures  
11 or multiple exposures.

12 And there are of course hypotheses  
13 partially tested about chronic exposures  
14 leading to neurobehavioral changes for some  
15 classes of pesticides. So, that also plays  
16 into the potential usefulness of those  
17 incident reports.

18 The other general comment about  
19 surveillance, which I think this really is, is  
20 that I think just to remember that a number of  
21 rare cancers were detected and associated with  
22 environmental exposures through occupational

1 surveillance. Not through formal quantitative  
2 epidemiology studies, initially, but through  
3 the reporting of angiosarcoma in vinyl  
4 chloride workers or bone cancers in radium  
5 dial painters or mesotheliomas in asbestos  
6 workers.

7                   So, that's another form of  
8 surveillance that applies the occupational  
9 setting rather than the incident reporting  
10 data here that's being discussed, but  
11 certainly historically was very, very  
12 important in identifying early human  
13 carcinogens.

14                   CHAIR HEERINGA: Thank you, Dr.  
15 Reif.

16                   Dr. Reed.

17                   DR. REED: One of the kind of case  
18 study that we also cover to have through the  
19 literature search and find them and use them,  
20 is the clinical case report in the open  
21 literature, because there's usually a lot of  
22 follow-up when - by the time that they



1 reported it. And I think for OP, that is an  
2 important source for chronic neurological  
3 sequella out of a single exposure.

4 And so although it's not mentioned  
5 as part of the database for incidents data, I  
6 think that's something that we used a lot or  
7 at least look into and see if there's  
8 something useful too. So, I would encourage  
9 the agency to look into that.

10 Maybe I'm pretty sure you already  
11 do, but not a part of this database, maybe.

12 CHAIR HEERINGA: Other  
13 contributions from panel members on the  
14 subject of the use of incident databases?

15 One obvious concern, and I think  
16 you've evaluated that, you're very close to  
17 these data sources, is that sometimes  
18 definitions change or - I think particularly  
19 in the ecological, I remember the carbofuran  
20 SAP. There was a historic, and I think it was  
21 mostly voluntary, record of incidents  
22 involving avian species.

1                   And they lost funding and states  
2   dropped in and out. So, there are these  
3   variations in terms of the consistency of the  
4   actual tracking.

5                   That's been brought out by others,  
6   but it's clearly part of understanding these  
7   data, too.

8                   Other comments on the - okay.  
9   Well, we'll have an opportunity again to  
10   revisit any thoughts that you have on any of  
11   the parts of Questions 1 through 3, but it's  
12   been a long day and I'm looking around the  
13   room. I don't want to say you look tired, but  
14   you don't look as spry as you did at 8:30 this  
15   morning.

16                  So, let me just turn to Dr.  
17   Manibuson or to Sarah. Any questions or  
18   clarifications that you'd like on -

19                  DR. MANIBUSAN: No. I just  
20   appreciate all the comments. They're pretty  
21   much right on target.

22                  I do want to express some

1 limitations from a few things that I heard in  
2 terms of recommendations for specimen  
3 collection.

4 I think it's really difficult to  
5 require that information from anyone to submit  
6 voluntarily. Because, again, these are  
7 probably cases are voluntarily called in to  
8 registrants or to NIOSH SENSOR or the  
9 different databases, and also to follow up on  
10 the need for understanding chronic effects  
11 through better follow-up.

12 Again, I know from discussions  
13 with ATSDR on the National Incident Database,  
14 that is a shortcoming of every database that  
15 we've talked about and that we've included.

16 The ability to follow up requires  
17 additional resources, and there's also privacy  
18 issues, people wanting to be contacted in the  
19 future.

20 A lot of things to consider, a lot  
21 of limitations, but we thank you for your  
22 comments.

1 CHAIR HEERINGA: At this point,  
2 then, I'll turn to our designated federal  
3 officials to see if there's any other  
4 administrative --

5 (Off the record comment.)

6 CHAIR HEERINGA: Just again to sort  
7 of reiterate, I think the proposed plan is  
8 that we will address Question Number 4  
9 tomorrow and wrap up with the formal  
10 proceeding by the noon hour.

11 The panel will then have a writing  
12 session tomorrow afternoon. And if the panel  
13 would be willing to meet with me just for five  
14 minutes afterwards in the breakout room, we'll  
15 discuss.

16 With that, I'd like to bring this  
17 afternoon's session to a close, and we'll plan  
18 to see everybody again tomorrow morning at  
19 8:30. Thanks to everyone for your  
20 participation today, and safe travels.

21 (Whereupon, the above-entitled  
22 matter was adjourned at 4:25 p.m.)

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